

FDA Briefing Document

Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

October 16, 2019

Cefiderocol Injection

Applicant: Shionogi, Inc.

Proposed Indication: The treatment of complicated urinary tract infections (cUTI), including pyelonephritis due to Gram-negative bacteria in patients with limited or no alternative treatment options

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought cefiderocol to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Introduction

This briefing document describes the review of safety and efficacy data for cefiderocol (S-649266), prepared by the FDA for the panel members of the Antimicrobial Drugs Advisory Committee. The FDA would like the committee to discuss whether the data are adequate to support the safety and efficacy of cefiderocol for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis in patients with limited or no alternative treatment options. We are also interested in any other issues the committee considers relevant.

2 Background

Complicated urinary tract infections (cUTIs) are associated with a functional or anatomical abnormality of the urinary tract, catheterization, or an underlying disease that interferes with host defenses. Pyelonephritis is considered a subset of cUTI. The most common causative Gram-negative bacterial pathogens include Enterobacteriaceae (primarily *Escherichia coli* and *Klebsiella pneumoniae*) and non-fermenting pathogens (*Pseudomonas aeruginosa*).

Between 2000 and 2009, the frequency of hospitalizations in the US for cUTI increased by about 50% for multi-drug resistant (MDR) *P. aeruginosa* and by about 300% for extended-spectrum beta-lactamase (ESBL)-producing organisms.¹

3 Product Information

Cefiderocol is a structurally modified cephalosporin antibacterial drug that utilizes a siderophore-based mechanism for bacterial cell entry. The proposed dosing regimen for the treatment of cUTI is 2 grams intravenously (IV) every 8 hours and dosage adjustments for altered renal function are shown in Table 3-1.

The infusion time is 3 hours and the proposed treatment duration is 7-14 days. Table 3-1 is presented on the following page.

Table 3-1: Proposed Dosing Regimen for Cefiderocol

Renal Function Category	Dose
Augmented renal clearance (CLcr \geq 120 mL/min)	2 gm IV every 6 hours
Normal renal function (CLcr 90 to < 120 mL/min) or Mild renal impairment (CLcr 60 to < 90)	2 gm IV every 8 hours
Moderate renal impairment (CLcr 30 to < 60 mL/min)	1.5 gm IV every 8 hours
Severe renal impairment (CLcr 15 to < 30 mL/min)	1 gm IV every 8 hours
ESRD (CLcr < 15 mL/min) or intermittent HD	0.75 gm IV every 12 hours
Patient with CVVH	1 gm IV every 12 hours
Patient with CVVHD or CVVHDF	1.5 gm IV every 12 hours

CLcr = creatinine clearance estimated by Cockcroft-Gault equation; ESRD = end stage renal disease; HD = hemodialysis; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CVVHDF = continuous venovenous hemodiafiltration

^a Cefiderocol is removed by hemodialysis (HD); thus, administer cefiderocol at the earliest possible time after HD on HD days

4 Key Regulatory History and Clinical Development

Cefiderocol was granted both fast track and Qualified Infectious Disease Product (QIDP) designations in 2015 for the following indications: cUTI, hospital acquired bacterial pneumonia (HABP), ventilator associated bacterial pneumonia (VABP), and bloodstream infections (bacteremia).

The Agency agreed that an adequate and well-controlled trial in cUTI with a noninferiority margin no larger than 15% would support a limited use indication. In the NDA, the Applicant submitted data from a trial comparing cefiderocol with imipenem-cilastatin (IMP) for the treatment of cUTI to support the indication for the treatment of cUTI including pyelonephritis in patients with limited or no alternative treatment options.

The Applicant also conducted a trial (CREDIBLE-CR trial) of cefiderocol compared with the best available therapy in infections caused by carbapenem resistant pathogens at various anatomical sites. The trial was ongoing at the time of the NDA submission and the enrollment was completed during the NDA review cycle. The trial completed enrollment and data were submitted to the NDA during the review cycle. Results of this trial from the datasets submitted to the Agency are included in the briefing document. The final clinical study report was not available at the time of this review.

The Applicant also conducted a Phase 3 trial (APEKS-NP trial) comparing cefiderocol with meropenem for the treatment of HABP/VABP. The trial was completed during the NDA review cycle; however, as data from this trial have not yet been submitted to the NDA, only top line results from the APEKS-NP study are included in this briefing document.

5 Clinical Pharmacology

Pharmacokinetics

In healthy subjects, the mean cefiderocol C_{max} was 89.7 mg/L and AUC was 386.1 mg·hr/L following a single IV dose of 2 grams infused over 3 hours. Cefiderocol exposure were similar after single and multiple doses, as expected based on the short terminal half-life (2-3 hours). The geometric mean (%CV) cefiderocol volume of distribution is 18.0 (18.1) L. Protein binding, primarily to albumin, of cefiderocol is 40.8% to 60.4% in human plasma. The geometric mean (%CV) cefiderocol clearance is 5.18 (17.2) L/hr. Cefiderocol is minimally metabolized, in vitro. Cefiderocol is primarily eliminated by the kidneys. The amount of cefiderocol excreted as unchanged drug in the urine is 90.6% of the administered dose.

Specific Populations

No clinically significant differences in the pharmacokinetics of cefiderocol were observed based on age, sex, or race/ethnicity.

Patients with Renal Impairment

Following a single IV dose of 1 gram cefiderocol infused over 1 hour, the mean cefiderocol AUC in subjects with CL_{Cr} 30-59 mL/min and 15-29 mL/min increased by 2.3 and 3.2-fold, respectively, compared to subjects with CL_{Cr} 90-119 mL/min. The mean cefiderocol AUC in ESRD subjects increased by 4.7-fold compared to subjects with CL_{Cr} 90-119 mL/min. Accordingly, cefiderocol dosage adjustment is recommended in patients with CL_{Cr} 59 mL/min or less (see

Table 3-1). There is no significant change (<30%) in the mean cefiderocol AUC between subjects with CLcr 60-89 mL/min and subjects with CLcr 90-119 mL/min, suggesting dosage adjustment is not needed for subjects with CLcr 60-89 mL/min.

Patients with CLcr \geq 120 mL/min

Increased cefiderocol clearance has been observed in patients with CLcr \geq 120 mL/min. A 2 gram dose of cefiderocol every 6 hours infused over 3 hours is predicted to provide cefiderocol exposures comparable to those in patients with CLcr 90-119 mL/min who receive cefiderocol 2 grams every 8 hours infused over 3 hours.

Patients with Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of cefiderocol is unknown. Hepatic impairment is not expected to alter the elimination of cefiderocol as hepatic metabolism/excretion represents a minor pathway of elimination for cefiderocol. No dose adjustment in subjects with hepatic impairment is proposed.

Drug-Drug Interactions

There are no known clinically significant cytochrome P450 or drug transporter mediated drug-drug interactions for cefiderocol.

Cefiderocol PK/PD Target and Probability Target Attainment Analyses

The percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the minimum inhibitory concentration (% $T_{CF>MIC}/\tau$) against the infecting organism best correlates with antibacterial activity in neutropenic murine thigh and lung infection models with Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*.

The Applicant proposed 75% $T_{CF>MIC}/\tau$ as the PK/PD target of cefiderocol required for 1-log₁₀ bacterial reduction based on a neutropenic murine thigh infection model. Note that the PK/PD target of cefiderocol required for 1-log₁₀ bacterial reduction in neutropenic murine lung infection model was 65% $T_{CF>MIC}/\tau$. The probability of target attainment (PTA) analyses conducted by the Applicant showed that >90% of simulated subjects achieved the PK/PD target up to MIC of 4 mcg/mL with the Applicant's proposed dosing regimens (see Table 3-1).

6 Microbiology

Mechanism of Action

The primary mechanism of action of cefiderocol is inhibition of peptidoglycan synthesis. It has been hypothesized that cefiderocol structural modifications, such as the addition of a catechol-moiety, and other modifications to specific side chains of the cephem nucleus result in enhanced transport across the outer membrane of Gram-negative bacteria. Specifically, cefiderocol binds to ferric ion and is actively transported into the periplasmic space by the outer membrane iron transport system in susceptible Gram-negative bacteria. The drug can also enter the bacteria by passive diffusion.

In vitro activity:

The *in vitro* activity of cefiderocol is impacted by the free iron concentration in the medium. Therefore, susceptibility testing is conducted in iron-depleted cation adjusted Mueller Hinton broth (ID-CAMHB). The iron concentration in ID-CAMHB is 0.02 mg/L and is similar to the concentration of non-transferrin bound iron in human serum. The cefiderocol MIC₉₀ against Gram-negative bacteria from surveillance studies conducted between 2014 and 2016 were ≤ 2 mcg/mL, Table 6-1. High MIC values were apparent for some isolates of certain species, particularly for *Enterobacter cloacae*, and *A. baumannii*. In the surveillance studies, the cefiderocol MIC₉₀ values for meropenem-resistant Enterobacteriaceae and multidrug resistant (resistant to meropenem, amikacin and ciprofloxacin) *P. aeruginosa* and *A. baumannii* were 4 to 8-fold higher compared to susceptible isolates.

Table 6-1: Cefiderocol MICs for target pathogens from surveillance studies

Gram-negative bacteria (no. of isolates)	Cefiderocol MIC ₉₀ (MIC Range) in mcg/mL
Enterobacteriaceae	
<i>Escherichia coli</i> (n = 5139)	0.5 (≤ 0.002 to 8)
Meropenem non-susceptible <i>E. coli</i> (n = 72)	2.0 (0.015 to 4)
<i>Klebsiella pneumoniae</i> (n = 4627)	1.0 (≤ 0.002 to 8)
Meropenem non-susceptible <i>K. pneumoniae</i> (n = 689)	4.0 (0.004 to 32)
<i>Klebsiella oxytoca</i> (n = 1434)	0.25 (≤ 0.002 to 4)
Meropenem non-susceptible <i>K. oxytoca</i> (n = 31)	1.0 (0.03 to 4)
<i>Enterobacter cloacae</i> (n = 1800)	1.0 (≤ 0.002 to 128)
<i>Enterobacter aerogenes</i> (n = 1017)	0.5 (≤ 0.002 to 8)
Meropenem non-susceptible <i>Enterobacter spp.</i> (n = 159)	8.0 (0.06 to 32)
<i>Citrobacter freundii</i> complex (n = 931)	0.5 (≤ 0.002 to 8)
<i>Citrobacter koseri</i> (n = 517)	0.5 (0.008 to 8)
Meropenem non-susceptible <i>Citrobacter spp.</i> (n = 32)	2.0 (0.015 to 8)
<i>Serratia marcescens</i> (n = 2382)	0.5 (≤ 0.002 to 32)
Meropenem non-susceptible <i>S. marcescens</i> (n = 38)	2.0 (0.015 to 4)
Non-fermenters	
<i>Pseudomonas aeruginosa</i> (n = 4942)	0.5 (≤ 0.002 to 8)
MDR <i>P. aeruginosa</i> (n = 262)	2.0 (0.002 to 32.0)
<i>Acinetobacter baumannii</i> (n = 2896)	2.0 (≤ 0.002 to >256)
MDR <i>A. baumannii</i> (n = 368)	8.0 (0.015 to >256)
<i>Stenotrophomonas maltophilia</i> (n = 1173)	0.25 (≤ 0.002 to 64)
MDR <i>S. maltophilia</i> (n = 218) [#]	0.25 (0.015 to >256)
Proteaceae	
<i>Proteus mirabilis</i> (n = 819)	0.12 (≤ 0.002 to >256)
<i>Proteus vulgaris</i> (n = 537)	0.12 (≤ 0.002 to 0.5)
<i>Providencia rettgeri</i> (n = 341)	0.12 (≤ 0.002 to >256)
<i>Morganella morganii</i> (n = 697)	0.25 (≤ 0.002 to > 256)

Meropenem non-susceptible was defined as meropenem MIC ≥ 2 mcg/mL for Enterobacteriaceae and ≥ 4 mcg/mL for non-fermenters. MDR = multidrug resistant (resistant to meropenem (MIC ≥ 4 mcg/mL), amikacin (MIC ≥ 64 mcg/mL) and ciprofloxacin (MIC ≥ 4 mcg/mL))

[#]There are no breakpoints for meropenem, amikacin and ciprofloxacin for *S. maltophilia*. Isolates were selected based on MDR definition for non-fermenters.

Source: Study Report S-649266-EB-344-N and Study Report S-649266-EF-115-N

The cefiderocol MIC₉₀ value against ESBL producing Enterobacteriaceae and non-fermenters were 2 to 4-fold higher than the non ESBL producing Enterobacteriaceae and non-fermenters.

The ratio of the minimum bactericidal concentration (MBC) to MIC suggests that cefiderocol is bactericidal against some strains of *E. coli* and *K. pneumoniae* and bacteriostatic against *S. marcescens* and non-fermenters such as *P. aeruginosa* and *A. baumannii*. In time kill studies, exposure of some Gram-negative bacteria to cefiderocol results in regrowth after initial killing. For *E. coli* NIH JC-2 (MIC=0.25 mcg/mL), sustained killing was observed at 2xMIC over 24 hours. For *K. pneumoniae* SR2291 (MIC = 0.008 mcg/mL), sustained killing was observed at 8 to 16x MIC. Sustained killing over 24 hours was not observed for *P. aeruginosa* ATCC 27853 (0.06 mcg/mL) and *A. baumannii* 17978 (MIC = 0.016 mcg/mL).

An increase in cefiderocol MIC was observed (0.063 to 2 mcg/mL and 0.016 to 2 mcg/mL) in *P. aeruginosa* and *A. baumannii* when parent and regrowth strains were tested.

Bacterial regrowth was confirmed in the in vitro pharmacodynamic chemostat model using the simulated human dose of cefiderocol, Table 6-2. Cefiderocol MIC increase was observed in the regrowth strains compared to parent strain for *E. cloacae* (8 to >32 mcg/mL), *S. marcescens* (2 to >32 mcg/mL), *A. baumannii* (1 to 32 mcg/mL; 2 to >32 mcg/mL). The cefiderocol MICs decreased when tested in combination with avibactam.

Table 6-2: In vitro bactericidal activity of cefiderocol with 2 g every 8 hours as a 3-hour infusion at 24 and 72 hours

Bacteria	Strain	Resistance Gene	Meropenem MIC (mcg/mL)	Cefiderocol MIC (mcg/mL)	≥ 3 log ₁₀ CFU/mL reduction	
					24 hours	72 hours
<i>E. cloacae</i>	1100876	NA	0.06	8.0	Not achieved	Not achieved
<i>E. coli</i>	1266865	NA	>32.0	2.0	Achieved	Achieved
<i>K. pneumoniae</i>	1217624	NA	4.0	4.0	Achieved	Not achieved
<i>K. pneumoniae</i>	856565	NA	16.0	2.0	Achieved	Achieved
<i>K. pneumoniae</i>	1217609	NA	16.0	2.0	Not achieved	Not achieved
<i>K. pneumoniae</i>	866349	NA	≤0.03	4.0	Achieved	Achieved
<i>K. pneumoniae</i>	1088960	NA	32.0	2.0	Achieved	Achieved
<i>S. marcescens</i>	659481	NA	0.06	2.0	Not achieved	Not achieved
<i>A. baumannii</i>	730770	NA	4.0	2.0	Not achieved	Not achieved
<i>A. baumannii</i>	1217591	NA	32.0	1.0	Achieved	Not achieved
<i>K. pneumoniae</i>	VA-384	KPC	64	4.0	Achieved	Not tested
<i>K. pneumoniae</i>	8667	KPC	>64	2.0	Achieved	Not tested
<i>E. coli</i>	DU 48916	NDM	64	4.0	Achieved	Not tested
<i>E. coli</i>	DS474	NDM	>64	16.0	Achieved	Not tested
<i>P. aeruginosa</i>	SR27001	IMP	>64	2.0	Achieved	Not tested
<i>P. aeruginosa</i>	NUBL-7808	VIM-2	>64	0.5	Achieved	Not tested
<i>A. baumannii</i>	NCTC 13424	CC92, OXA-23	16	1.0	Achieved	Not tested
<i>A. baumannii</i>	NCTC 8626	MDR, OXA-23	32	16.0	Achieved	Not tested

NA = not available

Source: Study Reports S-649266-EB-225-N and S-649266-EB-145-N

In vivo activity: The *in vivo* activity of cefiderocol was examined in murine infection models (neutropenic thigh, pneumonia, and immunocompetent urinary tract infection).

As with other beta-lactams %T > MIC is the major PK/PD parameter determining activity. This section focuses on the immunosuppressed models (when available) to allow for an unconfounded assessment of the *in vivo* activity of cefiderocol.

In the murine systemic infection model (AmpC producing *E. cloacae*, *S. maltophilia* and *B. cepacia*), the 50% cefiderocol effective (ED₅₀) dose was lower than comparators (cefepime, ceftazidime-avibactam (CAZ/AVI), meropenem or colistin).

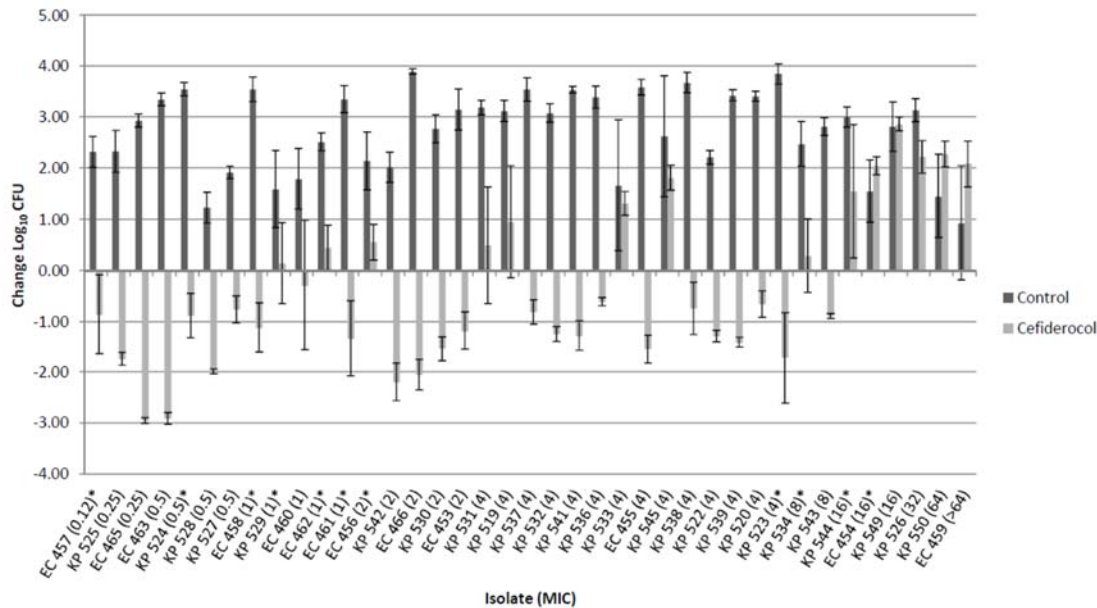
In the murine neutropenic lung infection model, cefiderocol was more active against KPC producing *K. pneumoniae* than CAZ/AVI. The data on the activity of cefiderocol against mice infected with bacteria expressing metallo- β -lactamases (IMP, NDM) are uninterpretable as the comparators (CAZ/AVI and/or meropenem) showed reduction in bacterial burden even though the comparators do not possess activity against metallo- β -lactamases. It is hypothesized that the current murine models may not be suitable for studying certain Zn⁺² dependent metallo- β -lactamases due to either a lack of expression or degradation of the enzyme under low Zn⁺² conditions observed during infections in mice.

In the immunocompetent murine urinary tract model, the activity of cefiderocol was comparable to that of CAZ/AVI against meropenem resistant KPC producing *K. pneumoniae* VA-357. Against *A. baumannii* strain carrying OXA-40 and OXA-51, the reduction in bacterial burden in the kidneys (1.77 log₁₀) was lower with cefiderocol than that with CAZ/AVI (3 log₁₀ reduction). Against cefepime-resistant *P. aeruginosa* (cefepime MIC 16 mcg/mL), the activity of cefiderocol was comparable to meropenem. The data on the activity of cefiderocol against *E. coli* ALL (NDM-1 containing) and *K. pneumoniae* (IMP-6 containing) are uninterpretable as the comparators (CAZ/AVI and/or meropenem) showed reduction in bacterial burden even though the comparators do not possess activity against metallo β - lactamases.

In the neutropenic thigh infection model, the activity of cefiderocol against 95 Gram-negative bacterial isolates (*P. aeruginosa*, *A. baumannii*, *E. coli*, and *K. pneumoniae*) was examined using humanized regimens of cefiderocol (2 gm q8h, 3- hour infusion). In Figure 6.1, the data show a ≥ 1 log₁₀ reduction in bacterial burden in the thighs was observed for 10/17 *E. coli* and *K. pneumoniae* isolates with cefiderocol MIC of ≤ 2 mcg/mL and 6/14 isolates with cefiderocol MIC of 4 mcg/mL. Cefiderocol was not effective for isolates with MIC of ≥ 8 mcg/mL.

In Figure 6.1, the data show a ≥ 1 log₁₀ reduction in bacterial burden in the thighs was observed for 10/17 *E. coli* and *K. pneumoniae* isolates with cefiderocol MIC of ≤ 2 mcg/mL and 6/14 isolates with cefiderocol MIC of 4 mcg/mL. Cefiderocol was not effective for isolates with MIC of ≥ 8 mcg/mL.

Figure 6.1: Mean absolute growth or reduction in log₁₀CFU \pm SD at 24 hours from starting inoculum by cefiderocol against *E. coli* and *K. pneumoniae* in the neutropenic murine thigh infection model



MIC, minimum inhibitory concentration; SD, standard deviation; EC, *E. coli*; KP, *K. pneumoniae*
Each * represents the number of times the isolate was repeated. All repeat data were averaged together.

Source: Study Report S-649266-EF-231-R

For *A. baumannii*, a ≥ 1 log₁₀ reduction in bacterial burden in the thighs was observed for 11/15 isolates with cefiderocol MIC of ≤ 2 mcg/mL and 1/1 isolates with cefiderocol MIC 4 mcg/mL. Cefiderocol was not effective for isolates with MIC of ≥ 8 mcg/mL.

For *P. aeruginosa*, a ≥ 1 log₁₀ reduction in bacterial burden in the thighs was observed for 10/16 isolates with cefiderocol MIC of ≤ 2 mcg/mL and 4/4 isolates with cefiderocol MIC 4 mcg/mL. Cefiderocol was not effective for isolates with MIC of 8 mcg/mL.

In a subset of 15 isolates that showed growth with cefiderocol at 24 hours and had pretreatment cefiderocol MICs of ≤ 8 mcg/mL, testing was repeated in the neutropenic thigh infection model, and post-treatment MICs were determined. Three of the 15 isolates (AB147, AB97, and KP 545) demonstrated a ≥ 4 -fold increase in cefiderocol MIC post-exposure compared to pre-exposure MICs, Table 6-3. The isolates AB147, AB97, and KP545 were not characterized further.

Table 6-3: Pre-exposure and post-exposure minimum inhibitory concentrations of cefiderocol against *P. aeruginosa*, *A. baumannii*, *E. coli* and *K. pneumoniae* isolates

Isolate	Pre-exposure cefiderocol MIC (mcg/mL)	Post-exposure cefiderocol MIC (mcg/mL)
EC 456	2	1
EC 462	1	2
KP 531	4	4
KP 519	4	4
KP 533	4	4
KP 545	4	64
KP 534	8	8
KP 529	1	1
AB 147	2	>256
AB 152	1	4
AB 97	8	>256
PSA 1564	0.25	0.5
PSA 1566	1	4
PSA 1572	2	4
PSA 1588	8	8

MIC, minimum inhibitory concentration; EC, *Escherichia coli*; KP, *Klebsiella pneumoniae*; PSA, *Pseudomonas aeruginosa*; AB, *Acinetobacter baumannii*

545: KPC3, SHV12, andTEM-OSBL

Source: Study Report S-649266-EF-231-R

A 4-fold increase in cefiderocol MIC was observed for a post-exposure *E. coli* isolate (EC 462) in a separate experiment where pharmacodynamic assessments were conducted over 72 hours in the neutropenic thigh infection model.² This isolate had a deletion in the RNA poly(A) polymerase gene *pcnB*, that could lead to changes in expression in multiple systems, including downregulation of the ferrichrome receptor operon *fhuABCD*.

Resistance

The frequency of resistance development in Gram negative bacteria exposed to cefiderocol at 10xMIC ranged from 10^{-6} to 10^{-8} . Increases in cefiderocol MIC from 4 mcg/mL to 32 mcg/mL were observed in purified IMP-1 producing *P. aeruginosa* mutants obtained during serial passage over 10 days.

Resistance to cefiderocol in Gram negative bacteria can arise due to mutations in genes involved in siderophore synthesis and regulation, iron uptake, membrane transport, two component signal transduction systems, regulation of AmpC β -lactamase production, penicillin binding proteins, efflux, and active transport. Reduced efficacy of cefiderocol was observed in murine lung infection using cefiderocol resistant mutants obtained from KPC-producing *K. pneumoniae* VA-384 carrying *envZ* mutation (osmolarity sensor protein) and NDM-1-producing *K. pneumoniae* NCTC13443 carrying *exbD* and *yicM* mutations (membrane spanning transporters).

Whole genome sequence analysis was performed on bacterial isolates with low susceptibility to cefiderocol obtained from surveillance studies. Most of these isolates carried an extended-spectrum β -lactamase (ESBL: PER-1, SHV-12 or TEM-10) and/or at least 1 carbapenem-hydrolyzing OXA-type β -lactamase (OXA-23, OXA-66, OXA-69 or OXA-72, OXA-82, OXA-50). *K. pneumoniae* isolates harbored a metallo-type carbapenemase (NDM-1) and/or an ESBL (CTX-M-15). In *E. aerogenes*, an endogenous-type AmpC β -lactamase was identified.

The beta-lactamase inhibitors, avibactam, clavulanic acid, and dipicolinic acid decreased the MICs of cefiderocol against Gram-negative bacteria with low susceptibility to cefiderocol (MIC \geq 8 mcg/mL), suggesting that the low-susceptibility to cefiderocol is due to serine- and metallo-type β -lactamases.

The risk for development of resistance was examined in an *in vitro* pharmacodynamic model where the time concentration curves of cefiderocol human dose (2 gm administered as 3-hour infusion) were simulated. Bacterial regrowth was observed within 24 to 72 hours for some strains (e.g., NDM-1 producing *K. pneumoniae* NCTC 13443, *E. cloacae* 1100876, *K. pneumoniae* 1217624, *K. pneumoniae* 1217609, *A. baumannii* 730770, and *A. baumannii* 1217591) after an initial ≥ 3 log₁₀ kill at 4-8 hours. For *S. marcescens* 659481, cefiderocol showed 1 log₁₀ CFU/mL reduction in bacterial counts at 8 hours followed by bacterial regrowth. Although an increase in cefiderocol MIC was observed, the increases were not stable on passage.

7 Clinical Development Program

Table 7-1 summarizes the clinical development program. The overall number of subjects exposed to cefiderocol was 761. The cUTI and APEKS-NP trials excluded patients with a Gram-negative infection caused by a carbapenem-resistant pathogen, if known at randomization. The CREDIBLE-CR trial exclusively enrolled patients with carbapenem-resistant organisms across body sites, including cUTI. The total number of subjects treated with cefiderocol for cUTI was 326, including 300 subjects in the cUTI and 26 subjects in the CREDIBLE-CR trial.

Table 7-1: Clinical Development Program of Cefiderocol

Trials (N)	Cefiderocol (N1)	Active Control (N1)	Total (N1)
Phase 1 (6)	212	NA	232*
cUTI (1)	300	148	448
CREDIBLE-CR (1)	101	49	150
APEKS-NP (1)	148	150	298
Total	761	346	1129

Source: Adapted from Applicant Table 2.7.4-1

* 20 subjects received placebo alone

N = Number of trials, N1 = Number of patients in the safety population

8 Trial in Complicated UTI

8.1 Study Design

The assessment of safety and efficacy for the treatment of cUTI was mainly based on the single trial titled “A Multicenter, Double-blind, Randomized, Clinical Study to Assess the Efficacy and Safety of Intravenous S-649266 in Complicated Urinary Tract Infections with or Without Pyelonephritis or Acute Uncomplicated Pyelonephritis Caused by Gram-negative Pathogens in Hospitalized Adults in Comparison with Intravenous IMP.” The clinicaltrials.gov identifier is NCT02321800. The first subject visit was in February 2015, the last subject completed the study in August 2016.

Key inclusion criteria were as follows:

- Hospitalized male and female subjects 18 years and older
- Diagnosis of cUTI, i.e., UTI with a history of at least 1 of the following: indwelling urinary catheter or recent instrumentation of the urinary tract; urinary retention caused by benign prostatic hypertrophy; urinary retention of at least 100 mL or more of residual urine after voiding; obstructive uropathy; azotemia caused by intrinsic renal disease, with or without pyelonephritis, or acute uncomplicated pyelonephritis, i.e., pyelonephritis and normal urinary anatomy (uncomplicated pyelonephritis was limited to $\leq 30\%$ of study population)
AND
- At least 2 of the following signs or symptoms: chills or rigors associated with fever; flank pain or suprapubic pain; nausea or vomiting; dysuria, urinary frequency, or urinary urgency; costovertebral angle tenderness
AND
- Urinalysis evidence of pyuria demonstrated by 1 of the following: dipstick analysis positive for leukocyte esterase; ≥ 10 white blood cells (WBCs) per μL in unspun urine, or ≥ 10 WBCs per high power field in spun urine.
- Positive urine culture within 48 hours prior to randomization that contained $\geq 10^5$ colony-forming units (CFUs)/mL of a Gram-negative uropathogen likely to be susceptible to imipenem (IMP). Patients could be randomized before availability or urine culture results.

Subjects who had been treated previously with an empiric antibacterial drug other than the study drugs but failed treatment, both clinically and microbiologically, were eligible for the study if they had an identified Gram-negative uropathogen that was not susceptible to the previously used empiric treatment and likely to be susceptible to IMP (or other alternative carbapenem).

Subjects receiving antibacterial prophylaxis for UTI who presented with signs and symptoms consistent with an active new UTI were enrolled provided all other eligibility criteria were met including obtaining a pretreatment qualifying baseline urine culture.

Key exclusion criteria were as follows:

- Subject's urine culture identified only a Gram-positive pathogen (not contaminant) suspected by Gram stain and/or identified a Gram-negative uropathogen resistant to imipenem.
- Subject's urine culture at study entry isolated more than 2 uropathogens, regardless of colony count, or subject had a confirmed fungal urinary tract infection.
- Subjects with asymptomatic bacteriuria.
- Subject was receiving hemodialysis or peritoneal dialysis.
- Subject received any amount of potentially therapeutic antibacterial drugs(s) for the treatment of the current cUTI within 96 hours prior to obtaining the study qualifying pretreatment baseline urine. Note: Approximately 25% of subjects with or without pyelonephritis could receive up to 24 hours of a potentially effective antibacterial drug (drugs with a dosing interval of 12 hours or less) during the previous 72 hours. Subjects who had objective documentation of clinical progression of cUTI while on antibacterial drugs or subjects who received antibacterial drugs for prophylaxis and then developed a cUTI were appropriate for enrollment.

Subjects were randomized in a 2:1 ratio to cefiderocol or IMP. Cefiderocol was given IV at a dose of 2 grams and IMP was given intravenously at a dose of 1 gram. Both cefiderocol and IMP were administered 3 times daily over 1 hour, at 8-hour intervals. The dosing regimens in both groups were adjusted for renal impairment and/or body weight. Both groups were treated with antibacterial therapy for 7 to 14 days in hospital. Oral step-down antibacterial therapy was not permitted.

Scheduled assessments included evaluations at the following study time points:

- An Early Assessment (EA) visit on Day 4±1 day
- An End of Treatment (EOT) visit
- A Test of Cure (TOC) visit 7±2 days after the EOT
- An Efficacy and Safety Follow-up (FUP) visit 14±3 days after the EOT
- A Safety Follow-up (EOS) visit 28±3 days after the EOT.

The primary efficacy variable in this study was a composite variable requiring both Clinical Response and Microbiological Eradication at the TOC visit:

- Clinical and Microbiological Response: Demonstration that the bacterial pathogen found at study entry was reduced to $<10^4$ CFUs/mL on urine culture at the TOC visit (Microbiological Eradication) and the resolution or improvement of the symptoms of cUTI present at study entry and no new symptoms (Clinical Response).
- Clinical and/or Microbiological Failure: Symptoms of cUTI present at study entry were not completely resolved or new symptoms developed, the subject died, or the urine culture taken at the TOC visit grew $\geq 10^4$ CFUs/mL of the original pathogen identified at study entry.

Secondary efficacy variables included the following:

- Composite of microbiological eradication and clinical response at the EA, EOT, and FUP visits
- Microbiological outcome per pathogen at the EA, EOT, TOC, and FUP visits
- Microbiological outcome per subject at the EA, EOT, TOC, and FUP visits
- Clinical outcome per subject at the EA, EOT, TOC, and FUP visits
- Clinical outcome per pathogen at the EA, EOT, TOC, and FUP visits

The statistical analysis plan included definitions for the following analysis populations:

- Intent-to-Treat (ITT) Population: All randomized subjects who received at least 1 dose of study drug. This population was analyzed according to randomized treatment.
- Microbiological Intent-to-Treat (Micro-ITT) Population: All subjects in the ITT Population who had a baseline Gram-negative bacterial uropathogen on culture of urine ($\geq 10^5$ CFUs/mL) or blood that caused the cUTI. This population was analyzed according to the randomized treatment.
- Safety Population: All randomized subjects who received at least 1 dose of study drug. This population was analyzed according to the treatment actually received.

This study was designed as a noninferiority trial. The noninferiority margin was 20% on the risk difference scale, and if meeting this criterion, the Applicant planned to sequentially test for a 15% margin. The Agency had agreed that an adequate and well-controlled trial in cUTI with a noninferiority margin no larger than 15% would support a limited use indication. Although this margin specified at the design stage was relatively wide, it was not directly relevant for the efficacy analysis because as will be discussed, cefiderocol met criteria for declaring statistical superiority. Based on the planned noninferiority margin and the need for a sufficient safety database, the planned sample size was 450 randomized subjects and 360 subjects in the Micro-ITT Population.

A total of 452 subjects were randomized, which closely matched the planned sample size of 450 subjects. Approximately 93% of subjects in each treatment group completed study assessments. Over 80% of randomized subjects in each treatment group belonged to the Micro-ITT Population, and thus had a baseline uropathogen. In this Micro-ITT Population used for the primary efficacy analysis, there were 290 subjects in the cefiderocol group and 147 subjects in the IMP group.

The subsequent table displays demographic characteristics in the Micro-ITT Population. Approximately half of subjects were over 65 years old, slightly over half were female, the large majority of patients were White, and the study was predominantly conducted in Eastern Europe. The cefiderocol and IMP treatment groups appeared to be relatively well balanced on demographic factors, Table 8-1.

Table 8-1 is presented on the following page.

Table 8-1: Demographics (Micro-ITT Population)

	Cefiderocol (n = 252) n (%)	IMP (n = 119) n (%)
Age (years)		
Mean (SD)	62 (16)	61 (18)
Median	66	66
(Min, Max)	(18, 93)	(18, 89)
<65	113 (44.8)	54 (45.4)
≥65	139 (55.2)	65 (54.6)
Gender		
Male	119 (47.2)	48 (40.3)
Female	133 (52.8)	71 (59.7)
Race		
White	241 (95.6)	115 (96.6)
Black	1 (0.4)	0 (0.0)
Asian	9 (3.6)	4 (3.4)
Hawaiian or Pacific Islander	1 (0.4)	0 (0.0)
Country		
Bulgaria	16 (6.3)	2 (1.7)
Czech Republic	25 (9.9)	6 (5.0)
Germany	1 (0.4)	1 (0.8)
Spain	2 (0.8)	0 (0.0)
Georgia	12 (4.8)	4 (3.4)
Croatia	21 (8.3)	15 (12.6)
Hungary	12 (4.8)	7 (5.9)
Italy	6 (2.4)	3 (2.5)
Japan	9 (3.6)	4 (3.4)
Latvia	5 (2.0)	2 (1.7)
Poland	44 (17.5)	20 (16.8)
Romania	56 (22.2)	33 (27.7)
Russia	39 (15.5)	21 (17.6)
United States	4 (1.6)	1 (0.8)

Source: Statistical reviewer and 1409R2121 Clinical Study Report Amendment 2, Table 14.1.1.5.3.

The following table displays additional baseline characteristics from the Micro-ITT Population. Most subjects had normal or mildly impaired baseline renal function, with slightly less than one fifth having moderately impaired renal function, and very few having severely impaired renal function. Slightly less than one half of subjects were diagnosed at baseline with cUTI without pyelonephritis, with the remaining subjects evenly split between those with cUTI with pyelonephritis and acute uncomplicated pyelonephritis. Approximately 90% of patients had no prior antibacterial therapy and approximately one third of patients were febrile at baseline. In line with inclusion criteria, major urinary symptoms were common at baseline. The two treatment groups appeared relatively balanced on the baseline characteristics considered.

Table 8-2: Baseline Characteristics (Micro-ITT Population) in the cUTI Trial

	Cefiderocol (n = 252) n (%)	IMP (n = 119) n (%)
Weight (kg)		
Mean (SD)	78 (16)	76 (18)
Median	78	73
(Min, Max)	(46, 146)	(42, 151)
Body mass index (kg/m ²)		
Mean (SD)	28 (5)	27 (7)
Median	27	26
(Min, Max)	(17, 45)	(18, 62)
Creatinine clearance (mL/min)		
>80 (normal)	124 (49.2)	51 (42.9)
>50 to 80 (mild)	78 (31.0)	41 (34.5)
30 to 50 (moderate)	41 (16.3)	23 (19.3)
<30 (severe)	7 (2.8)	4 (3.4)
Clinical diagnosis		
cUTI with pyelonephritis	65 (25.8)	29 (24.4)
cUTI without pyelonephritis	122 (48.4)	55 (46.2)
Acute uncomplicated pyelonephritis	65 (25.8)	35 (29.4)
Severity of disease		
Mild	26 (10.3)	11 (9.2)
Moderate	176 (69.8)	88 (73.9)
Severe	50 (19.8)	20 (16.8)
Prior antibacterial therapy*		
Yes	23 (9.1)	12 (10.1)
No	229 (90.9)	107 (89.9)
Reason for cUTI complication		
Indwelling urinary catheter	45 (17.9)	17 (14.3)
Prostatic hypertrophy	16 (6.3)	4 (3.4)
Neurogenic bladder	57 (22.6)	35 (29.4)
Obstructive uropathy	85 (33.7)	38 (31.9)
Azotemia	32 (12.7)	12 (10.1)
Baseline fever		
≥38° C	88 (34.9)	38 (31.9)
<38° C	164 (65.1)	81 (68.1)
Symptoms present		
Feeling feverish	135 (53.6)	60 (50.4)
Shaking/chills	128 (50.8)	63 (52.9)
Malaise	164 (65.1)	80 (67.2)
Urinary frequency	188 (74.6)	87 (73.1)
Urinary urgency	170 (67.5)	80 (67.2)
Dysuria	186 (73.8)	80 (67.2)
Urinary incontinence	50 (19.8)	25 (21.0)
Cloudy or change in urine color	191 (75.8)	99 (83.2)
Nausea	98 (38.9)	51 (42.9)
Vomiting	24 (9.5)	15 (12.6)

Pain above pubic bone	173 (68.7)	79 (66.4)
Abdominal pain	65 (25.8)	22 (18.5)
Flank pain	145 (57.5)	71 (59.7)
Back pain	78 (31.0)	39 (32.8)

Source: 1409R2121 Clinical Study Report Amendment 2, Tables 14.1.1.5.3 and 14.2.6.4.

*Taken 2 weeks prior to randomization for cUTI treatment, prophylaxis or treatment of other infection

The following table displays baseline pathogens in the Micro-ITT Population. The predominant pathogen was *E. coli* (over 60% of subjects in both treatment groups), followed by *K. pneumoniae* (approximately 20% of subjects in each treatment group). The cefiderocol and IMP groups had similar distributions of baseline uropathogens.

Table 8-3: Summary of Baseline Pathogens (Micro-ITT Population) in the cUTI Trial

	Cefiderocol (n = 252) n (%)	IMP (n = 119) n (%)
<i>Escherichia coli</i>	152 (60.3)	79 (66.4)
<i>Klebsiella pneumoniae</i>	48 (19.0)	25 (21.0)
<i>Proteus mirabilis</i>	17 (6.7)	2 (1.7)
<i>Pseudomonas aeruginosa</i>	18 (7.1)	5 (4.2)
Other	21 (8.3)	9 (7.6)

Source: Response to FDA Information Request dated 09 May 2019, Table 1.

Baseline pathogens in this trial were generally susceptible to the IMP comparator, based on *in vitro* susceptibility testing. For instance, all baseline *E. coli* isolates were susceptible to IMP. For *K. pneumoniae*, 87% of isolates in the cefiderocol group and 96% of isolates in the control group were susceptible to IMP. For other baseline pathogens, numbers were generally too small to provide meaningful summaries or comparisons.

The table below displays the duration of therapy in each treatment group of the Micro-ITT Population. Almost all patients received the recommended duration of 7 to 14 days of therapy. Treatment durations in the cefiderocol and IMP groups were similarly distributed.

Table 8-4: Summary of Treatment Duration (Micro-ITT Population) in the cUTI Trial

Days of treatment	Cefiderocol (n = 252) n (%)	IMP (n = 119) n (%)
<7	6 (2.4)	2 (1.7)
7	43 (17.1)	24 (20.2)
8	69 (27.4)	23 (19.3)
9	22 (8.7)	14 (11.8)
10	34 (13.5)	15 (12.6)
11	19 (7.5)	13 (10.9)
12	16 (6.3)	8 (6.7)
13	10 (4.0)	5 (4.2)
14	29 (11.5)	13 (10.9)
>14	4 (1.6)	2 (1.7)

Source: Statistical reviewer.

8.2 Efficacy Results

The table below displays results for the primary efficacy analysis of composite Clinical and Microbiological Outcome at the TOC visit in the Micro-ITT Population. In addition, the table displays the composite outcome at the Early Assessment, End of Treatment, and Follow-up visits.

Response rates for the primary endpoint were 183/252 (72.6%) for the cefiderocol group and 65/119 (54.6%) in the IMP group, leading to a point estimate for the difference in success rates of 18.6%, and a 95% confidence interval for the difference from 8.2% to 28.9%. Because the lower bound of this confidence interval exceeded zero, cefiderocol met statistical criteria for superiority to IMP, even though this study was designed as a noninferiority trial.

The interpretation of the primary efficacy analysis was not affected by indeterminate outcomes. The method of imputation least favorable to cefiderocol is to impute failure for subjects in the cefiderocol group with indeterminate outcomes but impute success for subjects in the control group with indeterminate outcomes. With this extremely conservative method of imputation, the success rates in the two groups become 183/252 (72.6%) for cefiderocol and 73/119 (61.3%) for IMP, and the 95% confidence interval would still fall above zero and thus meet criteria for superiority.

Although success rates were higher for the cefiderocol group than the control group at the TOC visit used for the primary efficacy analysis, response rates for the composite Clinical and Microbiological Outcome were similar between the two groups at the Early Assessment visit and End of Therapy visit, Table 8-5. In particular, success rates at the EOT visit were very high in both treatment groups.

Superiority results were not driven by resistance to IMP. As previously summarized in the discussion of baseline characteristics, few baseline uropathogens were resistant to IMP.

Table 8-5: Summary of Composite Clinical and Microbiological Outcome by Time Point (Micro-ITT Population) in the cUTI Trial

	Cefiderocol (n = 252) n (%)	IMP (n = 119) n (%)	Difference (%)	95% CI
Early Assessment				
Response	222 (88.1)	104 (87.4)	0.7	-6.5 to 7.8
Failure	24 (9.5)	11 (9.2)		
Indeterminate	6 (2.4)	4 (3.4)		
End of Treatment				
Response	243 (96.4)	114 (95.8)	0.7	-3.5 to 4.9
Failure	5 (2.0)	3 (2.5)		
Indeterminate	4 (1.6)	2 (1.7)		
Test of Cure				

Response	183 (72.6)	65 (54.6)	18.6	8.2 to 28.9
Failure	54 (21.4)	46 (38.7)		
Indeterminate	15 (6.0)	8 (6.7)		
Follow-up				
Response	137 (54.4)	47 (39.5)	15.3	4.7 to 25.9
Failure	92 (36.5)	49 (41.2)		
Indeterminate	23 (9.1)	23 (19.3)		

Source: 1409R2121 Clinical Study Report Amendment 2, Table 11-4.

With any composite endpoint, it is important to examine how results are driven by effects on individual components. Table 8-6 and Table 8-7 display results for secondary efficacy endpoints based on the Clinical Outcome at various time points, and the Microbiological Outcome at various time points.

Clinical cure rates were generally similar between cefiderocol and the IMP control group. However, sustained clinical cure rates trended higher for cefiderocol at the Follow-up visit. It is conceivable that clinical assessments at this time were influenced consciously or unconsciously by previous microbiological outcomes favoring cefiderocol, as patient symptoms at this visit were very similar between the treatment groups.

Microbiological eradication rates were similar between the two groups through the End of Therapy visit. High eradication rates are generally expected while patients are on therapy. However, eradication rates began to favor cefiderocol by the TOC visit. Therefore, it appeared that the main efficacy results in this trial were driven by a greater tendency for cefiderocol-treated patients to have suppressed pathogen growth after the end of treatment.

Table 8-6 : Summary of Clinical Outcome by Time Point (Micro-ITT Population) in the cUTI Trial

	Cefiderocol (n = 252) n (%)	IMP (n = 119) n (%)	Difference (%)	95% CI
Early Assessment				
Clinical Cure	228 (90.5)	108 (90.8)	-0.3	-6.6 to 6.1
Clinical Failure	23 (9.1)	10 (8.4)		
Indeterminate	1 (0.4)	1 (0.8)		
End of Treatment				
Clinical Cure	247 (98.0)	118 (99.2)	-1.1	-3.4 to 1.3
Clinical Failure	4 (1.6)	0 (0.0)		
Indeterminate	1 (0.4)	1 (0.8)		
Test of Cure				
Clinical Cure	226 (89.7)	104 (87.4)	2.4	-4.7 to 9.4
Clinical Failure	14 (5.6)	8 (6.7)		
Indeterminate	12 (4.8)	7 (5.9)		
Follow-up				
Sustained Cure	205 (81.3)	86 (72.3)	9.0	-0.4 to 18.4
Clinical Failure	19 (7.5)	13 (10.9)		

Clinical Relapse	12 (4.8)	12 (10.1)		
Indeterminate	16 (6.3)	8 (6.7)		

Source: 1409R2121 Clinical Study Report Amendment 2, Table 11-10.

Table 8-7: Summary of Microbiological Outcome by Time Point (Micro-ITT Population) in the cUTI Trial

	Cefiderocol (n = 252) n (%)	IMP (n = 119) n (%)	Difference (%)	95% CI
Early Assessment				
Eradication	232 (92.1)	109 (90.8)	1.3	-4.8 to 7.4
Failure	14 (5.6)	7 (5.9)		
Indeterminate	6 (2.4)	4 (3.4)		
End of Treatment				
Eradication	244 (96.8)	114 (95.8)	1.1	-3.0 to 5.3
Failure	3 (1.2)	3 (2.5)		
Indeterminate	5 (2.0)	2 (1.7)		
Test of Cure				
Eradication	184 (73.0)	67 (56.3)	17.3	6.9 to 27.6
Failure	53 (21.0)	44 (37.0)		
Indeterminate	15 (6.0)	8 (6.7)		
Follow-up				
Sustained Eradication	144 (57.1)	52 (43.7)	13.9	3.2 to 24.6
Failure	84 (33.3)	42 (35.3)		
Indeterminate	24 (9.5)	25 (21.0)		

Source: 1409R2121 Clinical Study Report Amendment 2, Table 11-8.

Among those patients with microbiological failure at TOC, the majority did not receive intravenous antibacterial drugs on or after the TOC visit. Five patients in the cefiderocol group and none in the IMP group received re-treatment. Table 8-8 summarizes these results.

Table 8-8: Summary of Administration of IV Gram-negative Antibacterial Drugs (Micro-ITT Population) in the cUTI Trial

Gram-negative antibacterial drugs on or after TOC	Cefiderocol (N=53) n (%)	IMP (N=44) n (%)
Yes	5 (9.4)	0
No	48 (90.6)	44 (100.0)

Source: Applicant response to IR dated March 13, 2019

The next two tables show results for the primary endpoint of Clinical and Microbiological response rate in demographic and baseline pathogen subgroups of the Micro-ITT primary analysis population. Numerical trends generally favored cefiderocol across subgroups defined by type of clinical diagnosis, age, gender, and pathogen.

Table 8-9: Summary of Composite Clinical and Microbiological Outcome at Test of Cure by Demographic Subgroups (Micro-ITT Population) in the cUTI Trial

	Cefiderocol n/N (%)	IMP n/N (%)	Difference (%)	95% CI
Overall	183/252 (72.6)	65/119 (54.6)	18.0	7.5 to 28.5
Clinical Diagnosis				
cUTI with Pyelonephritis	44/65 (67.7)	13/29 (44.8)	22.9	1.5 to 44.2
cUTI without Pyelonephritis	85/122 (69.7)	28/55 (50.9)	18.8	3.2 to 34.3
Acute Uncomplicated Pyelonephritis	54/65 (83.1)	24/35 (68.6)	14.5	-3.4 to 32.4
Age group				
<65 years	87/113 (77.0)	32/54 (59.3)	17.7	2.5 to 33.0
≥65 years	96/139 (69.1)	33/65 (50.8)	18.3	3.9 to 32.7
Gender				
Male	84/119 (70.6)	25/48 (52.1)	18.5	2.2 to 34.8
Female	99/133 (74.4)	40/71 (56.3)	18.1	4.4 to 31.8
Race				
White	175/241 (72.6)	64/115 (55.7)	17.0	6.3 to 27.7
Black or African American	0/1 (0.0)	0/0		
Asian	8/9 (88.9)	1/4 (25.0)	63.9	
Native Hawaiian or Other Pacific Islander	0/1 (0.0)	0/0		

Source: 1409R2121 Clinical Study Report Amendment 2, Table 11-6.

Table 8-10: Summary of Composite Clinical and Microbiological Outcome at Test of Cure by Baseline Pathogen Subgroups (Micro-ITT Population) in the cUTI Trial

Baseline pathogen	Response	
	Cefiderocol n/N (%)	IMP n/N (%)
<i>Escherichia coli</i>	113/152 (74.3)	45/79 (57.0)
<i>Klebsiella pneumoniae</i>	36/48 (75.0)	12/25 (48.0)
<i>Proteus mirabilis</i>	13/17 (76.5)	0/2 (0.0)
<i>Pseudomonas aeruginosa</i>	8/18 (44.4)	3/5 (60.0)
Other	17/21 (81.0)	5/9 (55.6)

Source: Statistical reviewer.

Seven patients in the cefiderocol group and 3 patients in the IMP group had a post-treatment 4-fold increase in MIC for the study drug, Table 8-11. None of these patients had a sustained response at FUP. One patient was given an IV antibacterial drug as rescue therapy for treatment of the baseline pathogen.

Table 8-11: 4-Fold Increase in MIC and Composite Outcomes in the cUTI Trial

Subject ID	Pathogen	MIC increase/ Study visit	Composite Outcome at TOC	Composite Outcome at FUP
Cefiderocol				
(b) (6)	<i>E. coli</i>	0.03 to 0.25/FUP	Response	Recurrence
	<i>E. cloacae complex</i>	0.12 to 0.5/TOC	Failure	Failure
	<i>E. coli</i>	0.25 to 1.0/FUP	Response	Recurrence
	<i>P. aeruginosa</i>	0.03 to 8.0/FUP	Response	Recurrence, re-infection with new <i>P.aeruginosa</i> strain
	<i>E. coli</i>	0.03 to 0.12/TOC	Failure	Failure
	<i>P. mirabilis</i>	0.06 to 0.5/TOC	Failure	Failure [†]
	<i>E. aerogenes</i>	0.015 to 0.12/FUP	Response	Recurrence
IMP				
(b) (6)	<i>E. coli</i>	0.12 to 0.5/FUP	Response	Recurrence
	<i>E. coli</i>	0.12 to 0.5/FUP	Indeterminate	Failure
	<i>P. aeruginosa</i>	1 to >8/TOC	Failure	Failure

Source: Medical Officer and Microbiology Reviewer

TOC – test of cure, FUP – follow-up, MIC – minimum inhibitory concentration

[†] Given IV amikacin at FUP

The subsequent table displays resolution of subject reported symptoms at the TOC visit in the Micro-ITT Population, which provides a summary of patient feeling and function. Most symptoms had completely resolved by the TOC visit, and rates of resolution appeared generally similar between the two treatment groups.

Table 8-12: Summary of Subject Reported Symptoms at TOC (Micro-ITT Population) in the cUTI trial

	Cefiderocol (n = 252)				IMP (n = 119)			
	None (%)	Mild (%)	Moderate (%)	Severe (%)	None (%)	Mild (%)	Moderate (%)	Severe (%)
Feeling feverish	99.6	0.0	0.4	0.0	99.1	0.9	0.0	0.0
Shaking/ Chills	99.6	0.0	0.4	0.0	99.1	0.9	0.0	0.0
Malaise	94.6	3.3	2.1	0.0	96.4	2.7	0.9	0.0
Urinary frequency	90.4	7.5	2.1	0.0	90.0	9.1	0.9	0.0

Urinary urgency	92.5	6.3	1.3	0.0	94.5	4.5	0.9	0.0
Dysuria	94.6	4.2	1.3	0.0	93.6	4.5	1.8	0.0
Urinary incontinence	94.2	3.8	1.3	0.8	92.7	6.4	0.0	0.9
Cloudy or urine color change	96.7	1.7	1.7	0.0	95.5	3.6	0.0	0.9
Nausea	98.3	0.4	1.3	0.0	97.3	0.9	1.8	0.0
Vomiting	99.6	0.4	0.0	0.0	99.1	0.0	0.9	0.0
Pain above pubic bone	96.3	2.5	1.3	0.0	93.6	4.5	1.8	0.0
Abdominal pain	99.2	0.8	0.0	0.0	99.1	0.9	0.0	0.0
Flank pain	96.3	2.9	0.8	0.0	95.5	3.6	0.9	0.0
Back pain	96.7	2.5	0.8	0.0	92.7	3.6	3.6	0.0

Note: For each symptom, <10% of subjects in each treatment group had missing outcomes, and percentages in this table are based on excluding these subjects.

Source: 1409R2121 Clinical Study Report Amendment 2, Table 14.2.6.4.

In summary, the trial supports the conclusion that cefiderocol is effective for the treatment of cUTI. Despite being designed as a noninferiority trial, results for the primary efficacy analysis of composite Clinical and Microbiological Outcome at the TOC visit in the Micro-ITT Population met statistical criteria for the superiority of cefiderocol compared to IMP. Clinical cure rates and resolution rates for individual symptoms were roughly similar between treatment groups across various time points. Microbiological outcomes were likewise similar between treatment groups through the End of Therapy visit, but favored cefiderocol by the TOC visit, reflecting a lower tendency for pathogen regrowth in the cefiderocol group.

However, the majority of patients with microbiological failure in the Micro-ITT population did not require re-treatment with IV antibacterial drugs. Thus, numerically favorable pathogen suppression in the cefiderocol group at TOC may not necessarily translate into enhanced clinical benefit. A 4-fold MIC increase was observed in seven cefiderocol-treated patients as compared to three imipenem-cilastatin-treated patients with a composite outcome of failure or recurrence at FUP.

8.3 Safety Results

The safety population consisted of 448 adults who received at least 1 dose of study drug. The maximum treatment duration was 14 days and treatment could be extended by 1 day if all infusions had not been given on Day 1. The mean total duration of exposure was 9.4 days in the cefiderocol group and 9.5 days in the IMP group. A similar percentage of patients received < 5 days (< 3%) and > 14 days (< 2%) of treatment in both groups. Over 90% of patients completed the study in each treatment group, and the most frequent reason for discontinuation was loss of follow-up.

Deaths

One death was reported in the cefiderocol group. This was a 76 year old white male with a medical history notable for diabetes mellitus complicated by chronic kidney disease, cerebrovascular disorder and hypertension, who was diagnosed with *E. coli* cUTI with concomitant bacteremia and azotemia. Death occurred on Day 7 after a sudden cardio-respiratory arrest, and the last dose of cefiderocol had also been administered on the same day. No other treatment-emergent adverse events (TEAEs) were reported. The Applicant assessed the death as not related to study drug, and more likely to be due to a vascular event given underlying risk factors. An autopsy had not been conducted.

Discontinuations

Discontinuations due to Adverse Events (AEs) were reported for 1.7% (5/300) subjects in the cefiderocol group and 2.0% (3/148) subjects in the IMP group as noted in Table 8-13.

Table 8-13: Treatment Discontinuation in the cUTI Trial (Safety Population)

Preferred Term	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any Discontinuation	5 (1.7)	3 (2.0)
Cardio-respiratory arrest	1 (0.3)*	0
Cardiac failure	0	1 (0.7)
Diarrhea	1 (0.3)	0
Drug hypersensitivity	1 (0.3)	0
Pneumonia	1 (0.3)	0
Abscess	0	1 (0.7)
Hepatic enzyme increased	1 (0.3)	0
Hematocrit decreased	0	1 (0.7)

Source: Medical Officer * Discontinuation due to death

The AEs leading to three discontinuations (hepatic enzyme increased, drug hypersensitivity, and diarrhea) in the cefiderocol group were moderate in severity and considered treatment-related by the investigator.

The patient with ‘hepatic enzyme increased’ was a 32 year old female with no prior medical history and normal baseline liver tests who had acute uncomplicated pyelonephritis. On Day 4, the AST was > 5x ULN, ALT was > 4x ULN, and GGT was >4x ULN. Cefiderocol was discontinued on Day 8 due to the event. On Day 9, the AST was ≥ 1x to < 2x ULN and the ALT was ≥ 2x ULN. The total bilirubin (TB) remained within the normal range, and PT and INR were slightly above ULN on Day 9. The AST, ALT, PT, and INR values resolved by Day 17. Confounders included an ongoing medication (levonorgestrel) and new medications (paracetamol (acetaminophen) on Day 2, drotaverine on Days 1-16, and metamizole sodium on Days 1-8).

The patient with ‘drug hypersensitivity’ had no prior history of allergy to β -lactam antibacterial drugs. The AE manifested as pruritis without other signs and symptoms, occurred after the first dose of cefiderocol, and resolved the same day after treatment with IV steroids. No new medications had been given. One patient developed diarrhea on Day 2 which resolved the same day after fluid and electrolyte repletion.

Serious Adverse Events

Serious Adverse Events (SAEs) were reported in 14 (4.7%) of subjects in the cefiderocol and 12 (8.1%) in the IMP group. Table 8-14 lists SAEs that occurred in ≥ 1 patient in the cefiderocol group. SAEs that occurred in one patient each in the IMP group were abscess, device related infection, prostatic abscess, pyelonephritis, acute kidney injury, hydronephrosis, lower gastrointestinal hemorrhage, gastrointestinal injury, alcohol poisoning, deep vein thrombosis, ischemic stroke, and congenital ureteric anomaly.

All cases of *C. difficile* may have been related to study drug given it is a known adverse reaction of β -lactam drugs. Two SAEs (anemia and anemia hemorrhagic) were of special interest given the potential effect of cefiderocol on iron metabolism/transport and concern for hematologic abnormalities. Both patients with anemia and hemorrhagic anemia were noted to have had duodenal ulceration resulting in gastrointestinal bleeding and had received anti-coagulants and non-steroidal anti-inflammatory drugs. Given these potential confounders, a causality assessment could not be made.

Table 8-14: SAEs Occurring in ≥ 1 Patient in Cefiderocol Group in the cUTI Trial

Preferred Term	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any SAE	14 (4.7)	12 (8.1)
Cardiac failure ^a	2 (0.7)	1 (0.7)
Anemia ^b	2 (0.7)	1 (0.7)
<i>Clostridium difficile</i> colitis	1 (0.3)	2 (1.4)
Diarrhea	1 (0.3)	1 (0.7) ^c
Ascariasis	1 (0.3)	0
Blood creatine phosphokinase increased	1 (0.3)	0
Cardio-respiratory arrest	1 (0.3)	0
Cellulitis	1 (0.3)	0
Duodenal ulcer	1 (0.3)	0
Gallbladder pain	1 (0.3)	0
Myocardial ischaemia	1 (0.3)	0
Pneumonia	1 (0.3)	0
Pyrexia	1 (0.3)	0
Renal abscess	1 (0.3)	0
Upper gastrointestinal hemorrhage	1 (0.3)	0
Urethrotomy	1 (0.3)	0
Urinary tract infection	1 (0.3)	0
Urinary tract obstruction	1 (0.3)	0

Source: Medical Officer

^aCardiac failure includes cardiac failure acute; ^banemia includes hemorrhagic anemia, hematocrit decreased
^cLaboratory sampling showed *C. difficile* Toxin A and B positive (CSR SAE narratives - page 1383)

Treatment-Emergent Adverse Events

The overall incidence rates for TEAEs were numerically lower in the cefiderocol group compared with the IMP group. Table 8-15 shows a summary of the most commonly reported TEAEs by treatment group. The incidence of rash, cough, and vomiting were numerically higher in the cefiderocol group compared with the IMP group. Cough occurred only in females in both groups. In the cefiderocol group, 3 of the 7 patients had underlying lung disease or confounding medications (angiotensin II receptor blocker); and the remaining had an unexplained cough. Cough and vomiting were both mild in severity in most cases. Rash and elevated liver laboratory tests are discussed in the section below.

Table 8-15: TEAEs in $\geq 2\%$ in Cefiderocol Group in the cUTI Trial

Preferred Term	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any TEAE	122 (40.7)	76 (51.4)
Diarrhea	13 (4.3)	9 (6.1)
Hypertension	13 (4.3)	8 (5.4)
Infusion site reactions ^a	11 (3.7)	7 (4.7)
Constipation	10 (3.3)	6 (4.1)
Rash ^b	9 (3.0)	1 (0.7)
Elevated liver laboratory tests ^c	7 (2.3)	1 (0.7)
Headache	7 (2.3)	8 (5.4)
Nausea	7 (2.3)	6 (4.1)
Cough	7 (2.3)	1 (0.7)
Candidiasis ^d	6 (2.0)	4 (2.7)
Hypokalaemia ^e	6 (2.0)	4 (2.7)
Vomiting	6 (2.0)	2 (1.4)

Source: Medical Officer

^a infusion site reactions includes infusion site erythema, inflammation, pain, or pruritis and injection site pain or phlebitis

^b rash includes erythema, skin irritation, rash macular, or rash maculo-papular

^c elevations in liver tests includes AST, ALT, ALP, GGT or hepatic enzyme increased

^d candidiasis includes oral or vulvovaginal candidiasis, candiduria

^e hypokalemia includes blood potassium decreased

Adverse Reactions of Special Interest and Submission Specific Safety Issues

Adverse events of interest include β -lactam class effects (rash/hypersensitivity reactions, gastrointestinal and liver toxicity, seizures and *C. difficile* colitis) and considerations related to cefiderocol (renal toxicity given its primary renal mode of excretion and iron transport/metabolism given its iron-chelation property).

Skin and Hypersensitivity

Nine (3.0%) subjects in the cefiderocol and 1 (0.7%) in the IMP group were reported to have had a rash when similar preferred terms (PTs) for rash (rash, rash macular, rash maculo-papular, skin irritation, and erythema) were combined. One patient in the cefiderocol group also had a mild photosensitivity reaction (dermatitis) on Day 1 which resolved the same day without treatment. As noted in the study discontinuations, one patient had drug hypersensitivity.

All rashes were mild in severity except in one patient who had a moderate rash (macular, disseminated); vancomycin was a confounding medication in that patient. Besides this disseminated rash, all other rashes were localized to the head, elbows, hands, face, or back. All cases of rash resolved except in one patient who developed a rash on Day 24 (10 days after cefiderocol was stopped). No new medications had been given concurrently. Despite treatment with steroids, the rash had not resolved by the end of the study.

Gastrointestinal

The most frequently reported AEs were diarrhea and constipation in both groups. TEAEs related to *C. difficile* were less frequently reported in the cefiderocol as compared to the IMP group. The Applicant proposes that the difference could be explained by the narrower spectrum of activity (no anaerobic or broad Gram-positive activity) as compared to IMP.

Neurologic

One patient (0.3%) in the cefiderocol group with a history of epilepsy had a TEAE of epileptic seizure of moderate severity. The patient had not been receiving concomitant anti-epileptic medication and developed a seizure on Day 7 that resolved with levetiracetam and diazepam. Cefiderocol was continued until day 10. No seizures were reported in the IMP group.

Hepatobiliary

Hepatic investigations (AST, ALT, ALP, GGT, and hepatic enzyme increased) were reported in 7 (2.3%) and 1 (0.7%) of cefiderocol and IMP-treated patients, respectively. There were no cases of Hy's Law in either treatment group. Two patients in the cefiderocol group had AST or ALT > 5x ULN. One discontinued treatment as discussed previously. The other patient was an 87 year old male with normal liver tests at baseline who developed AST >12x and ALT ≥19x on Day 21. Cefiderocol treatment ended on Day 9. Confounding medications included ongoing hydroxychloroquine sulfate and simvastatin, and new medications (fluconazole from Days 18-21 and amphotericin from Days 21-25) for candiduria. The liver ultrasound showed gallstones and sludge. The AST and ALT normalized by Day 39. The investigator considered the elevated liver tests as possibly related to fluconazole, but not to the study drug.

Four (1.3%) subjects in the cefiderocol group and 1 (0.7%) subject in the IMP group had an ALT or AST > 3x ULN. Table 8-16 shows maximum increases in liver tests post-baseline.

Table 8-16: Maximum Post-Baseline Increases in Liver Tests by Treatment group in the cUTI Trial

Baseline Value	Maximum Increase in Value	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
AST ≤ ULN	> 3x ULN to ≤ 5x ULN	1 (0.3)	1 (0.7)
	> 5x ULN to ≤ 20x ULN	2 (0.7)	0
ALT ≤ ULN	> 3x ULN to ≤ 5x ULN	2 (0.7)	0
	> 5x ULN to ≤ 20x ULN	1 (0.3)	1 (0.7)
ALT > ULN to ≤ 3x ULN	> 3x ULN to ≤ 5x ULN	1 (0.3)	0
TB ≤ ULN	>1.5x ULN to ≤ 3x ULN	0	3 (2.0)

Source: Medical Officer. AST – aspartate transferase, ALT – alanine transferase, TB – total bilirubin, ULN – upper limit of normal

The incidence of TEAEs in the gallbladder-related disorders SMQ (standardized medical dictionary for regulatory activities query for cholecystitis, cholecystitis chronic, cholelithiasis, and gallbladder pain) was 1.7% (5/300) in the cefiderocol group and 0% in the IMP group, Table 8-17. Four of these five patients treated with cefiderocol had no prior history of gall-bladder disorders. One of the five patients who had history of cholelithiasis developed gallbladder pain which was considered an SAE as it caused prolonged hospitalization. Information regarding surgical management was not available in any of the cases.

Although studies show minimal excretion of cefiderocol into bile, cholestasis from cefiderocol could not be excluded given the temporal association of this AE. Drug-induced gallbladder effects have been noted with other antimicrobial products such as ceftriaxone, erythromycin, ampicillin, and dapsone³.

Table 8-17: Hepatobiliary TEAEs in the cUTI Trial

Preferred Term	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Hepatobiliary TEAEs	6 (2.0)	3 (2.0)
Cholecystitis	2 (0.7)	0
Cholecystitis chronic	1 (0.3)	0
Cholelithiasis	1 (0.3)	0
Gallbladder pain	1 (0.3)	0
Hepatic cyst	1 (0.3)	0
Hepatic function abnormal	0	1 (0.7)
Hepatic lesion	0	1 (0.7)
Hepatic steatosis	1 (0.3)	0
Hepatomegaly	0	1 (0.7)

Source: Medical Officer

Coagulation

There was an imbalance in PT-INR elevation in the cefiderocol group as noted in the table below. The vitamin K antagonists (acenocoumarol, warfarin, warfarin potassium, and warfarin sodium) were reported as concomitant medications in more patients in the cefiderocol group, 5.7% (17/300) than in the IMP group, 2% (23/148). Of 20 patients with elevated INR during cefiderocol treatment, 16 had received concomitant anti-coagulant therapy and the maximum post-baseline INR among those patients was 4.0. The remaining 4 patients naïve to anti-coagulant therapy had transient increases in PT, INR, PTT and the maximum post-baseline INR was 1.9. Elevations in these coagulation tests were not associated with bleeding complications.

Table 8-18: Maximum Post-Baseline Increase in PT-INR in the cUTI Trial

Baseline Value of PT-INR	Maximum Increase in Value	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
≤ 1.5	> 1.5	5 (1.7)	1 (0.7)
≥ 1.5	> 1.5	13 (4.3)*	2 (1.4)

Source: Medical Officer; * 2 other patients treated with cefiderocol had INR ≥ 1.5 but baseline INR was missing.

Renal

The overall incidence of worsening in any stage of post-baseline eGFR was similar in both treatment groups, 14.0% (42/300) in the cefiderocol and 17.6% (26/148) in the IMP group, Table 8-19. The baseline and post-baseline stages by treatment group are noted in the table below. TEAEs reported within the renal and urinary disorders SOC were numerically higher in the IMP group, 8.8% (13/148), as compared to the cefiderocol group, 5.7% (17/300).

Table 8-19: Post-Baseline Worsening in eGFR* in the cUTI Trial

Baseline eGFR category	Post-baseline Worst Stage	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any Worse Stage		42 (14.0)	26 (17.6)
Stage 1	Stage 2	18 (6.0)	11 (7.4)
	Stage 3a	1 (0.3)	1 (0.7)
	Stage 4	0	1 (0.7)
Stage 2	Stage 3a	12 (4.0)	6 (4.1)
	Stage 3b	1 (0.3)	0
	Stage 4	0	1 (0.7)
Stage 3a	Stage 3b	8 (2.7)	3 (2.0)
Stage 3b	Stage 4	1 (0.3)	0
	Stage 5	1 (0.3)	0

Stage 4	Stage 5	0	3 (2.0)
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Source: Medical Officer

* Determined by the CKD EPI (Chronic Kidney Disease Epidemiology Collaboration Equation)

Stage 1: eGFR \geq 90, Stage 2 = eGFR 60-89, Stage 3a: eGFR 45-59, Stage 3b: eGFR 30-44, Stage 4: eGFR 15-29, Stage 5: eGFR $<$ 15

Hematologic

No clinically significant post-baseline changes in the mean hemoglobin, hematocrit, hepcidin-25, iron, total iron binding capacity, and transferrin saturation, were noted between treatment groups from screening to TOC. Four patients were reported to have anemia-related TEAEs in the cefiderocol group as compared to one in the IMP group. In the cefiderocol group, two patients had SAEs of anemia and hemorrhagic anemia as previously discussed. The other two patients had a prior history of anemia at baseline that did not appear to worsen while on cefiderocol.

9 Trial in Infections Caused by Carbapenem-Resistant Pathogens (CREDIBLE-CR)

9.1 Study Design

CREDIBLE-CR was titled “A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-Negative Pathogens.” The clinicaltrials.gov identifier for the study is NCT02714595.

As noted previously, this trial was ongoing at the time of the NDA submission. The trial completed enrollment and data were submitted to the NDA during the review cycle. Results of this trial from the available datasets submitted to the Agency are included in the briefing document. The final clinical study report has not yet been submitted for the Agency’s review.

The first patient was randomized and started study treatment on September 7, 2016, and the last patient was randomized and started study treatment on March 14, 2019. Patients enrolled in this trial had hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia/healthcare-associated bacterial pneumonia (HABP/VABP/HCABP), cUTI or bloodstream infections/sepsis (BSI/sepsis). A total of 152 patients were randomized in a 2:1 ratio to cefiderocol or best available therapy (BAT) control group.

The dosing regimen of cefiderocol was the same as in the cUTI study (2 grams IV every 8 hours with dosing adjustment for renal function), except that the infusion was given over 3 hours. Cefiderocol was given with or without adjunctive Gram-negative therapy. A single systemic antibacterial drug with Gram-negative activity (other than a polymyxin or a cephalosporin/carbapenem including combination with a β -lactamase inhibitor) was permitted for use as concomitant therapy in the cefiderocol group for patients with HABP/VABP/HCABP or BSI/sepsis. Cefiderocol dosing was adjusted by renal function.

The BAT regimen in the control group was the standard of care treatment as determined by the investigator based on an assessment of the patient's condition, the site of infection, causative organism, and susceptibility data. BAT consisted of 1 to 3 antibacterial drugs to treat carbapenem-resistant Gram-negative infections and was considered a treatment regimen rather than a study drug.

The duration of treatment with cefiderocol or BAT was to be 7 to 14 days. Based on investigator assessment, treatment could be extended up to 21 days if the reason for extension was documented. All study treatments were to be administered in the hospital. Patients enrolled in the trial were to be at least 18 years old and have clinically documented HABP/VABP/HCABP, cUTI, or BSI/sepsis caused by a Gram-negative pathogen with evidence of carbapenem resistance. Patients previously treated with an empirical antibacterial regimen were eligible if there was clinical and microbiological treatment failure.

Diagnosis of HABP/VABP/HCABP required new onset or worsening of pulmonary symptoms or signs, hypoxemia, need for acute changes in the ventilator support system, or respiratory secretions demonstrating evidence of inflammation and absence of contamination. In addition, HABP/VABP/HCABP patients were to have radiographic evidence of bacterial pneumonia and at least one of documented fever, hypothermia, leukocytosis, or leukopenia.

Diagnosis of cUTI required at least one of urinary retention caused by benign prostatic hypertrophy, neurogenic bladder, indwelling urinary catheter or recent instrumentation of the urinary tract, obstructive uropathy, or azotemia caused by intrinsic renal disease. Patients with cUTI additionally were to have two of the signs or symptoms of chills/rigors/warmth associated with fever, flank or suprapubic pain, nausea or vomiting, urinary frequency/urgency/dysuria, or costovertebral angle tenderness.

Patients with BSI were to have signs or symptoms associated with bacteremia and one or more positive blood cultures for a carbapenem-resistant Gram-negative pathogen consistent with the patient's clinical condition. BSI due to an endovascular source was disallowed.

Enrollment with sepsis required an identified infection site (e.g., severe skin infection, intra-abdominal infection) from which a carbapenem-resistant Gram-negative pathogen had been isolated using a clinical specimen. In addition, septic patients were to have two or more of oral or tympanic body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; tachycardia; tachypnea; or white blood cell count $>12,000$ cells/mm³, $<4,000$ cells/mm³, or $>10\%$ immature.

Exclusion criteria disallowed patients with coinfection caused by molds, central nervous system infections, requirement for >3 weeks of antibacterial treatment, cystic fibrosis or moderate to severe bronchiectasis, refractory septic shock, severe neutropenia, need for peritoneal dialysis, or APACHE II score >30 . Potentially effective prior antibacterial therapy was an exclusion criterion if received for a continuous duration of more than 24

hours in cUTI or 36 hours in HABP/VABP/HCABP or BSI/sepsis during the 72 hours leading to randomization.

Study visits included an early clinical/microbiological assessment (EA) visit on Day 3 to 4, an End of Treatment (EOT) visit on the last day of study treatment, a Test of Cure (TOC) visit 7 ± 2 days after the EOT visit, a Follow-Up (FUP) visit 14 ± 3 days after the EOT visit, and an End of Study (EOS) visit 28 ± 3 days after the EOT visit.

A Clinical Outcome of cure was defined as follows for EA, EOT, and TOC visits, and was measured by investigators without blinded assessors or an adjudication committee:

HABP/VABP/HCABP: Resolution or substantial improvement of baseline signs and symptoms of pneumonia including a reduction of SOFA and CPIS scores, and improvement or lack of progression of chest radiographic abnormalities such that no antibacterial therapy was required for the treatment of the current infection.

cUTI: Resolution or substantial improvement of baseline signs and symptoms of cUTI, or return to pre-infection baseline if known, such that no antibacterial therapy was required for the treatment of the current infection.

BSI/Sepsis: Resolution or substantial improvement of baseline signs and symptoms including a reduction in SOFA score, such that no antibacterial therapy was required for the treatment of BSI/sepsis. Patients with bacteremia must have had eradication of bacteremia caused by the Gram-negative pathogen.

A Microbiological Outcome of Eradication was defined by the following criteria at the EA, EOT, and TOC visit; an overall per patient outcome of eradication required these criteria to be met for each baseline pathogen:

HABP/VABP/HCABP: Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. If it was not possible to obtain an appropriate clinical culture and the patient had a successful clinical outcome, the response was presumed to be eradication.

cUTI: A urine culture showed the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFU/mL were reduced to $< 10^3$ CFU/mL.

BSI/Sepsis: Absence of the baseline Gram-negative pathogen from a blood culture and/or other primary source as applicable. In the case of sepsis, if the patient had a successful clinical outcome and it was not possible to obtain an appropriate clinical culture, the response was presumed to be eradication.

The primary efficacy endpoint was defined separately according to infection type:
For patients with HABP/VABP/HCABP or BSI/sepsis the primary efficacy endpoint was Clinical Outcome at the TOC visit.

For patients with cUTI the primary efficacy endpoint was Microbiological Outcome at the TOC visit.

Secondary efficacy endpoints included Clinical Outcome at various study visits, Microbiologic Outcome at various study visits, composite Clinical and Microbiological Outcome at various study visits, all-cause mortality at Day 14 and Day 28 for HABP/VABP/HCABP and BSI/sepsis, survival time for HABP/VABP/HCABP and BSI/sepsis, and a composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at the TOC visit.

The Safety population coincided with the Intent to Treat (ITT) population and was comprised of all randomized patients who received at least 1 dose of study drug. The primary efficacy analysis population for this trial was the Carbapenem-Resistant Microbiological Intent to Treat population (CR mITT). This was comprised of all patients with a baseline carbapenem-resistant Gram-negative pathogen from an appropriate clinical specimen. The Microbiological Intent to Treat population (Micro-ITT) was defined similarly to the CR Micro-ITT population but did not require baseline Gram-negative pathogens to be carbapenem-resistant.

This was to be a descriptively analyzed study without formal testing of statistical hypotheses. The planned sample size of 150 total patients was not based on formal power calculations. The protocol specified that a 95% confidence interval would be provided for each treatment group for the primary endpoint, and similar statistics were to be provided for secondary efficacy endpoints.

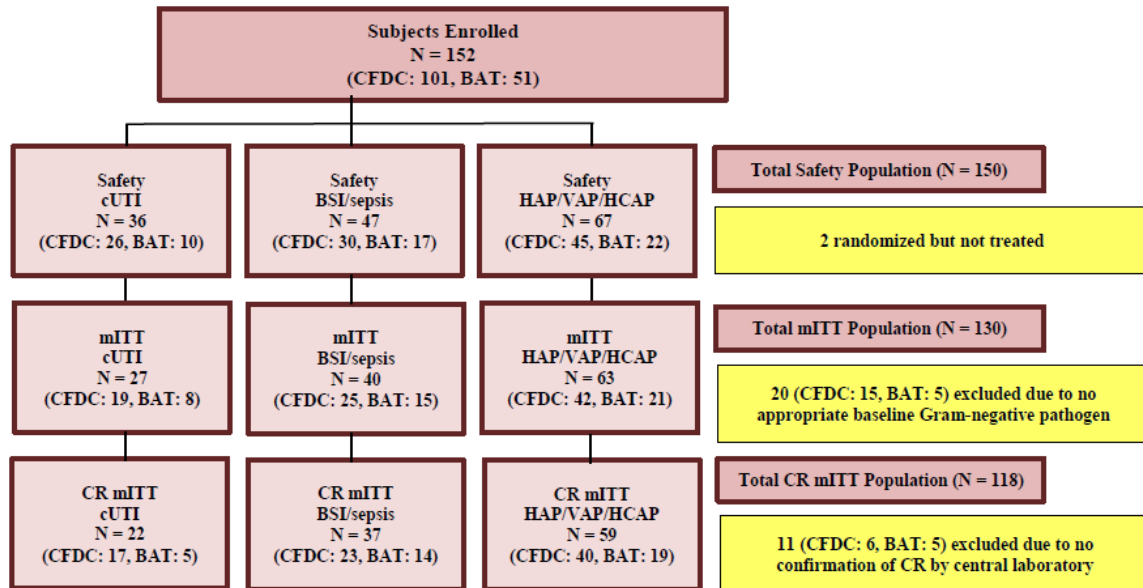
This was an open-label trial due to the difficulty of blinding with many potential BAT regimens in the control group. Furthermore, the Applicant was unblinded to ongoing results by treatment group and continuously monitored the trial. At the time of study initiation, the trial did not have an independent Data Safety Monitoring Board (DSMB).

On September 1, 2017 the Applicant first notified the Agency of unfavorable mortality rates in the ongoing study, which at the time were 6/25 (24.0%) in the cefiderocol group and 0/13 (0.0%) in the BAT control group. The Agency recommended that an independent DSMB monitor patient safety, and a DSMB subsequently monitored results for the remainder of the trial, and at each meeting recommended continued enrollment. The final sample size of 150 total treated patients was consistent with the originally planned sample size.

The Agency informed the Applicant at the design stage that this trial would likely not be adequate to support an indication. Some of the concerns raised by the Agency included the descriptive nature of the efficacy analysis, uncertainty regarding whether the clinical cure endpoint was sufficiently well-defined and reliable and potentially susceptible to open-label biases, the combining of cUTI patients with HABP/VABP/HCABP and BSI/sepsis patients, and the continuous monitoring of unblinded results by treatment group.

The disposition of patients is shown in the figure below. All but 2 of the 152 randomized patients were treated with study drug, and thus included in the Safety population. Of these patients there were 118/150 (79%) in the CR mITT population.

Figure 9.1: CREDIBLE-CR Patient Disposition



BAT = best available therapy; BSI = blood stream infection; CFDC = cefiderocol; CR = carbapenem resistant; CR mITT = Carbapenem-resistant Microbiological Intent-to-treat Population; cUTI = complicated urinary tract infection; HAP = hospital-acquired bacterial pneumonia; HCAP = healthcare-associated bacterial pneumonia; VAP = ventilator-associated bacterial pneumonia.

Source: CREDIBLE-CR Final Study Summary, Figure 1.

The subsequent table displays baseline characteristics for both the Safety and the CR mITT efficacy analysis populations. There were respectively 45%, 31%, and 24% of patients with diagnoses of HAP/VABP/HCABP, BSI/sepsis, and cUTI. Patients were predominantly male and either White or Asian. Slightly less than half of patients had a baseline APACHE II score ≥ 16 and over one third of patients had estimated creatinine clearance ≤ 50 mL/min. The most common baseline pathogens were *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*. The overall mean body mass index (BMI) was 25.4 kg/m², mean sequential organ failure assessment score (SOFA) was 5.1, and mean clinical pulmonary infection score (CPIS) was 4.8.

There were several baseline imbalances between the cefiderocol and BAT groups in this small trial, such as the cefiderocol group having a greater proportion of patients ≥ 65 years old and all 5 patients with *S. maltophilia* being randomized to cefiderocol. More patients with HAP/VABP/HCABP in the BAT group than in the cefiderocol group were ventilated at randomization (81.8% vs. 71.1%, respectively). A higher percentage of patients had prior antibacterial therapy in the 2 weeks before randomization in the BAT group than in the cefiderocol group (100% vs. 92.1%, respectively). A higher percentage of patients had bacteremia (in any clinical diagnosis group) in the BAT group as

compared to the cefiderocol group ([34.2% 13/38] vs. 27.5% [22/80], respectively) in the CR mITT population.

Table 9-1: CREDIBLE-CR Baseline Characteristics (Safety Population and CR mITT Population)

	Safety Population		CR mITT Population	
	Cefiderocol (N= 101) n (%)	BAT (N = 49) n (%)	Cefiderocol (N = 80) n (%)	BAT (N = 38) n (%)
Clinical diagnosis				
HABP/VABP/HCABP	45 (44.6)	22 (44.9)	40 (50.0)	19 (50.0)
BSI/Sepsis	30 (29.7)	17 (34.7)	23 (28.8)	14 (36.8)
cUTI	26 (25.7)	10 (20.4)	17 (21.2)	5 (13.2)
Age group				
<65 years	37 (36.6)	27 (55.1)	30 (37.5)	21 (55.3)
≥65 years	64 (63.4)	22 (44.9)	50 (62.5)	17 (44.7)
Gender				
Male	66 (65.3)	35 (71.4)	55 (68.8)	29 (76.3)
Female	35 (34.7)	14 (28.6)	25 (31.2)	9 (23.7)
Race				
White	63 (62.4)	32 (65.3)	48 (60.0)	27 (71.1)
Asian	29 (28.7)	14 (28.6)	24 (30.0)	9 (23.7)
Other	9 (8.9)	3 (6.1)	8 (10.0)	2 (5.3)
Baseline pathogen				
<i>A. baumannii</i>	39 (38.6)	17 (34.7)	37 (46.2)	17 (44.7)
<i>K. pneumoniae</i>	34 (33.7)	16 (32.7)	32 (40.0)	12 (31.6)
<i>P. aeruginosa</i>	17 (16.8)	12 (24.5)	17 (21.2)	11 (28.9)
<i>S. maltophilia</i>	5 (5.0)	0 (0.0)	5 (6.2)	0 (0.0)
APACHE II				
≤15	55 (54.5)	27 (55.1)	41 (51.2)	21 (55.3)
≥16	46 (45.5)	22 (44.9)	39 (48.8)	17 (44.7)
Region				
North America	6 (5.9)	3 (6.1)	4 (5.0)	3 (7.9)
South America	9 (8.9)	4 (8.2)	7 (8.8)	3 (7.9)
Europe	57 (56.4)	28 (57.1)	45 (56.2)	23 (60.5)
Asia-Pacific	29 (28.7)	14 (28.6)	24 (30.0)	9 (23.7)
Creatinine clearance (mL/min)				
<30 (severe)	20 (19.8)	7 (14.3)	15 (18.8)	3 (7.9)
30 to 50 (moderate)	23 (22.8)	8 (16.3)	18 (22.5)	6 (15.8)
>50 to 80 (mild)	20 (19.8)	12 (24.5)	15 (18.8)	9 (23.7)
>80 to <120 (normal)	18 (17.8)	10 (20.4)	15 (18.8)	9 (23.7)
≥120 (ARC)	20 (19.8)	12 (24.5)	17 (21.2)	11 (28.9)

Source: Statistical reviewer and Supporting TFLs for CREDIBLE-CR Study Summary, Tables 14.1.1.4.2 and 14.1.1.4.4. ARC = augmented renal clearance

Also, the frequency of hypotension, sepsis/septic shock, urinary tract infection, anemia, congestive heart failure, decubitus ulcer, and tobacco use was higher in the BAT group

and the frequency of atrial fibrillation and tracheostomy was higher in the cefiderocol group (difference in treatment groups was approximately 5% for each condition). Otherwise, baseline comorbidities noted were balanced.

The study population consisted of mostly patients enrolled in Europe and Asia-Pacific. There were 9/150 (6%) total patients enrolled in the US. Although the clinical characteristics of these patients were expected to be similar, intensive care practices may have varied across study sites. The BAT also varied by investigator and ranged from a single antibacterial drug to a combination regimen consisting of up to 3 drugs. Four patients in the BAT group received newer cephalosporin/ β -lactamase inhibitor combinations such as ceftolozane-tazobactam and ceftazidime-avibactam, and these patients were enrolled in the US and Spain. About 5 patients in each treatment group received combination therapy with tigecycline which is not approved for HABP/VABP/HCABP or cUTI and 4 patients in the BAT group received doripenem which is not approved for VABP. In the CR mITT population over 80% of patients in the cefiderocol group received cefiderocol as monotherapy, and approximately two thirds of patients in the BAT group were treated with colistin-based regimens. The next table displays the initial study drug regimens used in the cefiderocol group and BAT group on Day 1 and 2 for treatment of Gram-negative pathogens.

Table 9-2: CREDIBLE-CR Study Drug Regimens for Gram-negative Pathogens on Day 1 and 2 (CR mITT Population)

Study Drug Regimen	Cefiderocol (N = 80) n (%)	Study Drug Regimen	BAT (N = 38) n (%)
Cefiderocol	66 (82.5)	Colistin-based regimen	25 (65.8)
Cefiderocol + Adjunctive Therapy	14 (17.5)	Noncolistin-based regimen	13 (34.2)
Cefiderocol	66 (82.5)	Colistin	6 (15.8)
Cefiderocol, Tigecycline	4 (5.0)	Colistin, Tigecycline	3 (7.9)
Cefiderocol, Fosfomycin	2 (2.5)	Colistin, Ampicillin-sulbactam	2 (5.3)
Cefiderocol, Amikacin	1 (1.3)	Colistin, Fosfomycin	2 (5.3)
Cefiderocol, Ampicillin-sulbactam	1 (1.3)	Colistin, Amikacin	1 (2.6)
Cefiderocol, Ciprofloxacin	1 (1.3)	Colistin, Amikacin, Levofloxacin	1 (2.6)
Cefiderocol, Colistin	1 (1.3)	Colistin, Cefepime	1 (2.6)
Cefiderocol, Gentamicin	1 (1.3)	Colistin, Cefepime, Tigecycline	1 (2.6)
Cefiderocol, Gentamicin, Tigecycline	1 (1.3)	Colistin, Cefoperazone-sulbactam	1 (2.6)
Cefiderocol, Levofloxacin	1 (1.3)	Colistin, Ceftolozane-Tazobactam	1 (2.6)
Cefiderocol, Piperacillin-tazobactam	1 (1.3)	Colistin, Ertapenem	1 (2.6)
		Colistin, Imipenem-cilastatin	1 (2.6)
		Colistin, Meropenem	1 (2.6)
		Colistin, Piperacillin	1 (2.6)
		Colistin, Piperacillin-tazobactam	1 (2.6)
		Polymyxin B, Ampicillin-sulbactam, Fosfomycin	1 (2.6)
		Amikacin	1 (2.6)
		Amikacin, Ceftazidime-avibactam	1 (2.6)
		Amikacin, Doripenem	1 (2.6)
		Ceftazidime, Ciprofloxacin	1 (2.6)
		Ceftazidime-avibactam	1 (2.6)
		Ceftazidime-avibactam, Gentamicin	1 (2.6)
		Ciprofloxacin, Trimethoprim-sulfamethoxazole	1 (2.6)
		Doripenem	1 (2.6)
		Doripenem, Gentamicin	1 (2.6)
		Doripenem, Tobramycin	1 (2.6)
		Fosfomycin	1 (2.6)
		Gentamicin	1 (2.6)
		Imipenem-cilastatin, Tigecycline	1 (2.6)

Source: CREDIBLE-CR Final Study Summary, Table 2.

9.2 Efficacy Results

As previously discussed, the primary efficacy analysis in the CR mITT population was to be based on Clinical Outcome at the TOC visit for patients with HABP/VABP/HCABP/BSI/Sepsis and was to be based on Microbiological Outcome at the TOC visit for patients with cUTI. The tables below show both Clinical Outcome and Microbiological Outcome at the TOC for patients enrolled with all three infection types. There were no apparent

efficacy decrements based on either the clinical or microbiological endpoints. Clinical cure rates were approximately 50% in each treatment group in the CR mITT primary efficacy analysis population of patients with carbapenem-resistant baseline pathogens. Assessments of microbiological eradication rates were limited because approximately 50% of patients in each treatment group were classified as having an outcome of indeterminate. Efficacy assessments within the cUTI subgroup were additionally limited by the sample size of only 5 patients in the BAT control group.

Table 9-3: CREDIBLE-CR Summary of Clinical Outcome at the TOC visit by Clinical Diagnosis (CR mITT Population)

	Cefiderocol n/N (%)	BAT n/N (%)	Difference (%)	95% CI
Overall				
Clinical cure	42/80 (52.5)	19/38 (50.0)	2.5	-16.8 to 21.8
Clinical failure	27/80 (33.8)	14/38 (36.8)	-3.1	
Indeterminate	11/80 (13.8)	5/38 (13.2)	0.6	
HABP/VABP/HCABP				
Clinical cure	20/40 (50.0)	10/19 (52.6)	-2.6	-29.9 to 24.6
Clinical failure	16/40 (40.0)	6/19 (31.6)	8.4	
Indeterminate	4/40 (10.0)	3/19 (15.8)	-5.8	
cUTI				
Clinical cure	12/17 (70.6)	3/5 (60.0)	10.6	-37.5 to 58.7
Clinical failure	2/17 (11.8)	1/5 (20.0)	-8.2	
Indeterminate	3/17 (17.6)	1/5 (20.0)	-2.4	
BSI/Sepsis				
Clinical cure	10/23 (43.5)	6/14 (42.9)	0.6	-32.3 to 33.5
Clinical failure	9/23 (39.1)	7/14 (50.0)	-10.9	
Indeterminate	4/23 (17.4)	1/14 (7.1)	10.2	

Source: CREDIBLE-CR Final Study Summary, Table 6.

Table 9-4: CREDIBLE-CR Summary of Microbiological Outcome at the TOC visit by Clinical Diagnosis (CR mITT Population)

	Cefiderocol n/N (%)	BAT n/N (%)	Difference (%)	95% CI
Overall				
Eradication	25/80 (31.3)	9/38 (23.7)	7.6	-9.3 to 24.5
Persistence	16/80 (20.0)	10/38 (26.3)	-6.3	
Indeterminate	39/80 (48.8)	19/38 (50.0)	-1.3	
HABP/VABP/HCABP				
Eradication	9/40 (22.5)	4/19 (21.1)	1.4	-21.0 to 23.9
Persistence	8/40 (20.0)	7/19 (36.8)	-16.8	
Indeterminate	23/40 (57.5)	8/19 (42.1)	15.4	
cUTI				
Eradication	9/17 (52.9)	1/5 (20.0)	32.9	-9.4 to 75.3
Persistence	5/17 (29.4)	1/5 (20.0)	9.4	
Indeterminate	3/17 (17.6)	3/5 (60.0)	-42.4	
BSI/Sepsis				

Eradication	7/23 (30.4)	4/14 (28.6)	1.9	-28.4 to 32.1
Persistence	3/23 (13.0)	2/14 (14.3)	-1.2	
Indeterminate	13/23 (56.5)	8/14 (57.1)	-0.6	

Source: CREDIBLE-CR Final Study Summary, Table 13.

9.3 Safety Results

All safety analyses in this section were conducted in the safety population which was comprised of all randomized and treated patients.

Exposure

In the CREDIBLE-CR trial, 150 patients were exposed to study drugs (101 treated with cefiderocol and 49 treated with BAT). The total duration of treatment was 7-14 days, with extension up to 21 days if needed. For subjects with cUTI, a minimum of 5 days of therapy was allowed. The mean duration of exposure was 11.5 days for cefiderocol and 12.9 days for BAT for patients enrolled with HABP/VABP/HCABP and BSI/Sepsis. The mean duration of exposure was 11.5 days for cefiderocol and 7.6 days for BAT for patients enrolled with cUTI. In patients with cUTI, treatment was given for >14 days for 7/26 (27%) patients in the cefiderocol group and 0/10 (0%) patients in the BAT group.

Deaths

Survival status for each patient in the safety population was to be captured through the EOS visit 28 ± 3 days after the end of treatment, or when death was due to serious adverse events occurring prior to the EOS visit. The table below displays the distribution of patients with known or missing survival status by timepoint. There were no missing data through Day 28, but by Day 49 half of the patients had unknown survival status.

Table 9-5: Distribution of Missing Survival Status by Timepoint in the CREDIBLE-CR Trial

Timepoint	Total missing (n = 150) n (%)	Cefiderocol missing (n = 101) n (%)	BAT missing (n = 49) n (%)
Day 28	0 (0.0)	0 (0.0)	0 (0.0)
Day 35	13 (8.7)	7 (6.9)	6 (12.2)
Day 42	55 (36.7)	35 (34.7)	20 (40.8)
Day 49	75 (50.0)	48 (47.5)	27 (55.1)

Source: Statistical reviewer.

This section discusses all-cause mortality results at Day 14, Day 28, and Day 49. Assessments of Day 14 and Day 28 all-cause mortality were secondary objectives of the study, these assessments could be performed with no missing data, and the endpoints were driven by early deaths that may have been more closely related to infection and treatment failure. Day 49 mortality was assessed because it almost completely coincided with mortality through the EOS visit, with the difference being that it additionally

included one patient in the BAT group who died on Day 43 with unknown cause of death. The Day 49 all-cause mortality was analyzed because it included more events and because there were numerical trends with higher cefiderocol mortality at later times. However, Day 49 mortality results were limited by missing data.

After the EOS visit there were 2 deaths in the cefiderocol group (on Days 51 and 89) and 5 deaths in the BAT group (on Days 43, 53, 70, 106, and 108). Post-study deaths were discovered for reasons such as responses to AE queries and identifications in FDA inspection reports. Analyses of death at late times beyond the EOS visit are potentially limited by informative censoring in this open-label study.

The table below summarizes all-cause mortality at Day 14, Day 28, and Day 49 in the safety population. A detailed summary of all fatal cases in the table is also provided in the Appendix. The cefiderocol group had a higher rate of all-cause mortality than the BAT group at Day 14 and Day 28, and by Day 49 the mortality rates were 34/101 (33.7%) in the cefiderocol group and 10/49 (20.4%) in the BAT group. Confidence intervals for mortality differences did not provide nominally statistically significant evidence of a mortality increase at any time, but by Day 49 the confidence interval for the difference in mortality rates excluded a cefiderocol mortality benefit of 1.3% or more.

Table 9-6: All-Cause Mortality at Day 14, Day 28, and Day 49 in the CREDIBLE-CR Trial

Timepoint	Cefiderocol (n = 101)	BAT (n = 49)	Difference	95% CI
Day 14	19/101 (18.8)	6/49 (12.2)	6.6	-5.4 to 18.5
Day 28	25/101 (24.8)	9/49 (18.4)	6.4	-7.3 to 20.1
Day 49	34/101 (33.7)	10/49 (20.4)	13.3	-1.3 to 27.8

Note: The 95% confidence intervals in this table are based on handling mortality as a binary yes/no outcome, so can differ from confidence intervals based on Kaplan-Meier confidence intervals that also consider censoring.

Source: Statistical Reviewer and CREDIBLE-CR Final Study Summary, Table 21.

All-cause mortality at Day 14, Day 28, and Day 49 by time and infection site is presented in the table below. The greatest mortality imbalance disfavoring cefiderocol was noted in the HABP/VABP/HCABP subgroup at Day 49, followed by the BSI/Sepsis subgroup at Day 49. Numerically, the cUTI subgroup had a higher mortality in the BAT group, but the difference is difficult to interpret with a small sample size and wide confidence interval.

Table 9-7: All-Cause Mortality at Day 14, Day 28, and Day 49 by Clinical Diagnosis in the CREDIBLE-CR Trial

	Cefiderocol	BAT	Difference	95% CI
HABP/VABP/HCABP				
Day 14	11/45 (24.4)	3/22 (13.6)	10.8	-8.3 to 29.9
Day 28	14/45 (31.1)	4/22 (18.2)	12.9	-8.1 to 34.0
Day 49	19/45 (42.2)	4/22 (18.2)	24.0	2.4 to 45.7
BSI/Sepsis				
Day 14	5/30 (16.7)	1/17 (5.9)	10.8	-6.6 to 28.2
Day 28	7/30 (23.3)	3/17 (17.6)	5.7	-17.9 to 29.3
Day 49	11/30 (36.7)	4/17 (23.5)	13.1	-13.4 to 39.7
cUTI				
Day 14	3/26 (11.5)	2/10 (20.0)	-8.5	-36.1 to 19.2
Day 28	4/26 (15.4)	2/10 (20.0)	-4.6	-33.0 to 23.8
Day 49	4/26 (15.4)	2/10 (20.0)	-4.6	-33.0 to 23.8
HABP/VABP/HCABP + BSI/Sepsis				
Day 14	16/75 (21.3)	4/39 (10.3)	11.1	-2.2 to 24.4
Day 28	21/75 (28.0)	7/39 (17.9)	10.1	-5.7 to 25.8
Day 49	30/75 (40.0)	8/39 (20.5)	19.5	2.6 to 36.3

Source: Statistical Reviewer

Time-to-event analysis can provide more power than analysis of mortality at a fixed timepoint and is less dependent on the subjective timepoint cutoff. The hazard ratio analysis of time-to-death through Day 49 in the safety population is provided in the table below. The estimated hazard ratio of 1.77 was consistent with more rapid mortality for the cefiderocol group than the BAT group, but the two-sided p-value of 0.11 did not reach the level of a nominally statistically significant difference.

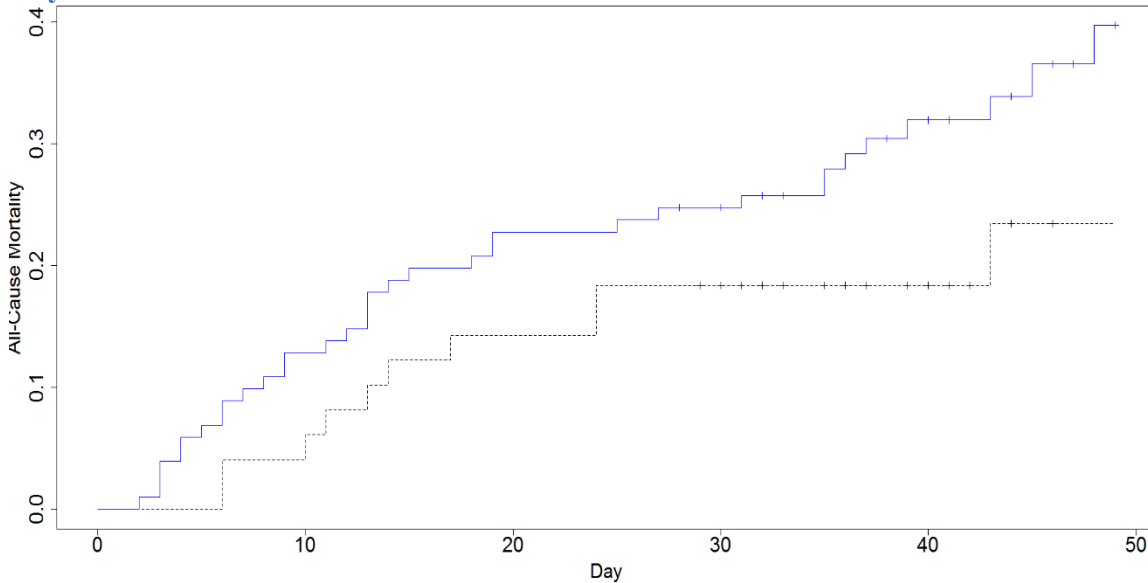
Table 9-8: Hazard Ratio Analysis of Time-to-Death through Day 49 in the CREDIBLE-CR Trial

Hazard ratio	95% CI	Two-sided p-value
1.77	0.87 to 3.57	0.11

Source: Statistical Reviewer

A Kaplan-Meier Plot of all-cause mortality in the safety population is displayed in the following figure. The mortality curves separated at an early time and cefiderocol mortality numerically exceeded the BAT mortality through Day 49.

Figure 9.2: Kaplan-Meier Plot of All-Cause Mortality by Treatment Group through Day 49 in the CREDIBLE-CR Trial



Blue Solid Line = Cefiderocol. Black Dashed Line = BAT.

Source: Statistical reviewer.

The following safety analyses related to mortality will focus on the 43 total deaths, exclusive of the additional death in the BAT group on Day 43 as discussed previously, in which the cause of death was unknown.

Table 9-9 shows the number of deaths based on the study day that the fatal TEAE occurred and the corresponding system organ class (SOC). Most deaths occurred within 15 days of the start of the study treatment in both groups and 9 additional deaths occurred past 30 days in the cefiderocol group. Also, most deaths were infection-related, and the frequency was higher in the cefiderocol group than in the BAT group (20.8% vs. 6.1%, respectively). Hepatobiliary-related deaths were also more common in the cefiderocol group than in the BAT group (2.0% vs. 0% respectively).

Table 9-9: TEAEs Associated with Deaths through Day 49 by System Organ Class in the CREDIBLE-CR Trial

	Cefiderocol (N = 101) n (%)				BAT (N = 49) n (%)			
	<15 days	15 to 30 days	>30 days	Total	<15 days	15 to 30 days	>30 days	Total
Number of Deaths	19 (18.8)	6 (5.9)	9 (8.9)	34 (33.7)	6 (12.2)	3 (6.1)	1 (2.0)	10 (20.4)

Primary SOC								
Infections and infestations	12 (11.9)	3 (3.0)	6 (5.9)	21 (20.8)	2 (4.1)	1 (2.0)	0	3 (6.1)
Renal and urinary	3 (3.0)	0	0	3 (3.0)	1 (2.0)	0	0	1 (2.0)
Cardiac	3 (3.0)	2 (2.0)	1 (1.0)	6 (5.9)	2 (4.1)	1 (2.0)	0	3 (6.1)
General and administration	2 (2.0)	0	1 (1.0)	2 (2.0)	2 (4.1)	1 (2.0)	0	3 (6.1)
Vascular	1 (1.0)	0	0	1 (1.0)	0	0	0	0
Hepatobiliary	1 (1.0)	0	1 (1.0)	2 (2.0)	0	0	0	0
Metabolism and nutrition	1 (1.0)	0	0	1 (1.0)	1 (2.0)	0	0	1 (2.0)
Respiratory, thoracic and mediastinal	1 (1.0)	3 (3.0)	0	4 (4.0)	2 (4.1)	0	0	2 (4.1)
Neoplasms	0	0	1 (1.0)	1 (1.0)	0	0	0	0
Unknown	0	0	0	0	0	0	1 (2.0)	0

Source: Medical Officer.

Moreover, the specific TEAEs that occurred at a higher frequency in the cefiderocol group were infection-related: septic shock, pneumonia (combined with bacterial pneumonia), sepsis, and bacteremia, as noted in Table 9-10.

Table 9-10: TEAEs Associated with Death through the EOS visit by Preferred Term in the CREDIBLE-CR Trial

Preferred Term	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
TEAEs leading to death	34 (33.7)	9 (18.4)
Septic shock	11 (10.9)	3 (6.1)
Pneumonia/bacterial pneumonia	6 (5.9)	0
Cardiac arrest	4 (4.0)	2 (4.1)
Sepsis	3 (3.0)	0
Respiratory failure/acute respiratory failure	2 (2.0)	1 (2.0)
Oliguria	2 (2.0)	0
Bacteraemia	2 (2.0)	0
Multi-organ failure	2 (2.0)	2 (4.1)
Shock	1 (1.0)	0
Anuria	1 (1.0)	0
Pneumonia aspiration	1 (1.0)	0
Cardiac failure congestive	1 (1.0)	0

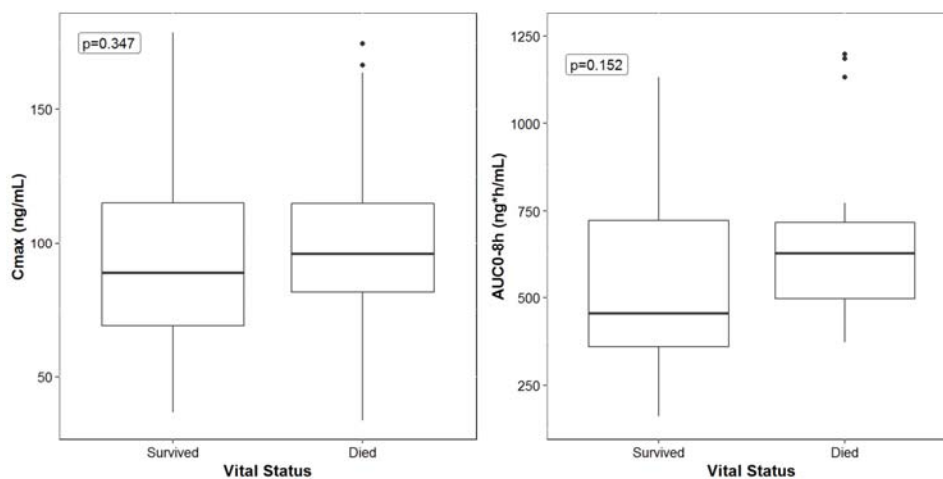
Chronic hepatic failure	1 (1.0)	0
Hepatic failure	1 (1.0)	0
Hyponatraemia	1 (1.0)	0
Hypotension	1 (1.0)	0
Lung neoplasm malignant	1 (1.0)	0
Myocardial infarction	1 (1.0)	0
Obstructive airways disorder	1 (1.0)	0
Acute kidney injury	1 (1.0)	1 (2.0)
Sudden death	1 (1.0)	0
General physical health deterioration	0	1 (2.0)
Device related infection	0	1 (2.0)
Bradycardia	0	1 (2.0)
Metabolic acidosis	0	1 (2.0)
Respiratory arrest	0	1 (2.0)

Source: Medical Officer

Comparison of Cefiderocol Exposures by Survival Status

In CREDIBLE-CR study, the steady-state cefiderocol C_{max} and AUC_{0-8h} (post-hoc estimates) in patients who survived (N=57) were comparable with those in patients who died (N=22) (Figure 9.3), indicating that there was no apparent association between cefiderocol exposure and death.

Figure 9.3: Comparisons of the C_{max} and AUC_{0-8h} between patients who survived (N=57) versus patients who died (N=22).



C_{max} was measured at the end of drug infusion at steady state. AUC_{0-8h} values were post-hoc estimates of AUC during a dosing interval at steady state.

Source: Clinical Pharmacology reviewer

Subgroup Analysis of Mortality

Several subgroups were examined based on demographic variables and clinical characteristics, Table 9-11. The following subgroups were associated with an absolute 10% higher mortality rate in the cefiderocol as compared to the BAT group at Day 49: clinical diagnosis of HABP/VABP/HCABP or BSI/Sepsis, male or female gender, age group ≤ 65 years or ≥ 75 years, Asian and “other” race, *A. baumannii* or *P. aeruginosa* baseline pathogen, APACHE II Score of ≥ 16 , Asia-Pacific or South American region, and normal renal function or mild to severe renal impairment groups, and the presence of bacteremia in any clinical diagnosis group at baseline.

Table 9-11: All-Cause Mortality at Day 49 by Baseline Subgroup in the CREDIBLE-CR Trial

	Cefiderocol (N=101) n/N (%)	BAT (N=49) n/N (%)	Difference (%)	95% CI
Clinical diagnosis				
HABP/VABP/HCABP	19/45 (42.2)	4/22 (18.2)	24.0	2.4 to 45.7
BSI/Sepsis	11/30 (36.7)	4/17 (23.5)	13.1	-13.4 to 39.7
cUTI	4/26 (15.4)	2/10 (20.0)	-4.6	-33.0 to 23.8
Age group				
<65 years	10/37 (27.0)	3/27 (11.1)	15.9	-2.7 to 34.5
≥ 65 years	24/64 (37.5)	7/22 (31.8)	5.7	-17.1 to 28.5
≥ 75 years	13/29 (44.8)	4/14 (28.6)	16.3	-13.5 to 46.0
Gender				
Male	23/66 (34.8)	8/35 (22.9)	12.0	-6.1 to 30.0
Female	11/35 (31.4)	2/14 (14.3)	17.1	-6.8 to 41.1
Race				
White	18/63 (28.6)	7/32 (21.9)	6.7	-11.5 to 24.9
Asian	14/29 (48.3)	3/14 (21.4)	26.8	-1.3 to 55.0
Other	2/9 (22.2)	0/3 (0.0)	22.2	
Baseline pathogen				
<i>A. baumannii</i>	19/39 (48.7)	4/17 (23.5)	25.2	-0.4 to 50.7
<i>K. pneumoniae</i>	8/34 (23.5)	4/16 (25.0)	-1.5	-27.0 to 24.1
<i>P. aeruginosa</i>	6/17 (35.3)	2/12 (16.7)	18.6	-12.4 to 49.6
<i>S. maltophilia</i>	4/5 (80.0)	0/0		
APACHE II score				
≤ 15	13/55 (23.6)	5/27 (18.5)	5.1	-13.3 to 23.6
≥ 16	21/46 (45.7)	5/22 (22.7)	22.9	0.3 to 45.6
Region				
North America	0/6 (0.0)	0/3 (0.0)	0.0	
South America	1/9 (11.1)	0/4 (0.0)	11.1	
Europe	19/57 (33.3)	7/28 (25.0)	8.3	-11.8 to 28.5
Asia-Pacific	14/29 (48.3)	3/14 (21.4)	26.8	-1.3 to 55.0
Creatinine clearance (mL/min) group				
<30 (severe)	8/20 (40.0)	2/7 (28.6)	11.4	
30 to 50 (moderate)	10/23 (43.5)	2/8 (25.0)	18.5	
>50 to 80 (mild)	9/20 (45.0)	3/12 (25.0)	20.0	-12.8 to 52.8

>80 to <120 (normal)	4/18 (22.2)	1/10 (10.0)	12.2	-14.5 to 39.0
≥120 (ARC)	3/20 (15.0)	2/12 (16.7)	-1.7	-27.9 to 24.6
Bacteremia status*				
Bacteremia	10/24 (41.7)	4/13 (30.8)	10.9	-21.0 to 42.8
No Bacteremia	22/62 (35.5)	5/31 (16.1)	19.4	1.8 to 36.9

Source: Statistical reviewer. ARC = augmented renal clearance

* primary or concomitant bacteremia in any clinical diagnosis subgroup. Bacteremia subgroups defined within the CR mITT Population rather than the Safety Population.

Development of Resistance to Study Drug

In 15 cefiderocol-treated patients, there was a 4-fold increase in cefiderocol MIC in one or more baseline pathogens, as noted in Table 9-12. Most of these patients had an unsuccessful outcome (either clinical failure at TOC or death before TOC). A fatal infection-related PT was noted in 60% (9/15). Eight patients with a fatal outcome had a clinical diagnosis of HABP/VABP/HCABP and one had sepsis due to VABP. The increases in MIC were noted at days ranging from Days 3 to 23. Eight deaths involved a 4-fold increase in cefiderocol MIC in a carbapenem-resistant non-fermenter (*A. baumannii*, *S. maltophilia*, and *P. aeruginosa*). Five of these patients with clinical failure by TOC received treatment with rescue IV antibacterial drugs and three of these patients died after the TOC visit.

Table 9-12: 4-fold MIC Increases in the Cefiderocol group in the CREDIBLE-CR Trial

Subject ID/ diagnosis	Pathogen	MIC (mcg/mL) at baseline	MIC (mcg/mL)/ Study Day	Outcome by TOC	Day of Death	Fatal PT
(b) (6)	<i>A. baumannii</i>	0.25	1.0 (Day 3)	Death	9	Non-resolved sepsis
(b) (6) VABP	<i>A. baumannii</i> [†]	1.0	8 (Day 10)	Death	24	Non-resolved sepsis
(b) (6) VABP	<i>S. maltophilia</i> [†]	0.06	0.25 (Day 8)	Death	8	Septic shock, hepatic failure
(b) (6) HABP	<i>A. baumannii</i> [†]	1.0	4.0 (Day 11)	Death	13	Aggravated pneumonia
	<i>P. aeruginosa</i>	0.25	2.0 (Day 11)			
(b) (6) VABP	<i>S. maltophilia</i>	0.06	0.25 (Day 14)	Death	15	Septic shock, cardiac arrest
(b) (6) Sepsis	<i>A. baumannii</i>	2	>64 (Day 16)	Cure	27	Secretion obstruction, hemoptysis
(b) (6) VABP	<i>A. baumannii</i>	0.25	4.0 (Day 14)	Failure*	39	Septic shock
(b) (6) VABP	<i>A. baumannii</i> [†]	1.0	8.0 (Day 15)	Failure*	45	Septic shock

(b) (6) HABP	<i>K. pneumoniae</i> [†]	0.25	2 (Day 23)	Failure*	31	Septic shock
(b) (6) VABP	<i>P. aeruginosa</i> [†]	0.5	2.0 (Day 16)	Failure*	Survived	NA
(b) (6) BSI	<i>E. coli</i> [†]	0.5	2 (Day 11)	Failure*	Survived	NA
(b) (6) cUTI	<i>K. pneumoniae</i>	0.12	0.5 (Day 17)	Cure	Survived	NA
(b) (6) cUTI	<i>P. aeruginosa</i>	0.12	2.0 (Day 22)	Cure	Survived	NA
(b) (6) VABP	<i>A. baumannii</i>	0.06	1.0 (Day 3)	Cure	Survived	NA
(b) (6) VABP	<i>K. pneumoniae</i> [†]	0.06	0.5 (Day 8)	Cure	Survived	NA

Source: Medical Officer

[†] more than 1 pathogen at baseline (other pathogens without 4-fold MIC increase)

* Treatment with rescue IV antibacterial drugs for initial Gram-negative infection

In the BAT group, in 5 patients there was a 4-fold MIC increase to any antibacterial drug in the regimen, most often to colistin. Of these 5 patients, two died and the remaining had clinical failure at TOC. Both patients who died had a carbapenem-resistant *K. pneumoniae* at baseline. One patient with BSI had a 4-fold increase in the colistin MIC on Day 13 and died on Day 17 due to septic shock. The other patient with a VABP had a 4-fold increase in the colistin and tigecycline MICs on Day 13 and died due to cardiopulmonary arrest on Day 25.

Mortality by Initial Treatment

Patients receiving cefiderocol plus adjunctive therapy had a higher mortality rate than those who received cefiderocol alone, Table 9-13. Of note, the patients who received cefiderocol and adjunctive therapy had a higher mean APACHE score than those receiving cefiderocol alone (18.1 vs. 14.8, respectively), and this may have contributed to the observed increased mortality.

Table 9-13: Mortality through Day 49 by Initial Study Drug Regimen at Day 1 and 2 in the CREDIBLE-CR Trial

Cefiderocol (N= 101) n/N (%)		BAT (N=49) n/N (%)	
Cefiderocol monotherapy	Cefiderocol + adjunctive therapy	Colistin based regimen	Non-colistin based regimen
25/86 (29.1)	9/15 (60.0)	8/30 (26.7)	2/19 (10.5)

Source: Statistical Reviewer

Adjudication committee results

An adjudication committee consisting of three external physicians (professors of medicine and infectious disease, intensive care, and internal medicine) was appointed by the Applicant to review blinded mortality data and categorize the cause of death. Death was first categorized by relatedness to the original Gram-negative infection. If the death was not directly related to the original infection, it was subcategorized into the following causes: underlying comorbidity, infection other than the original Gram-negative infection, drug-related AE, or iatrogenic cause. If the death was directly related to the original infection, it was subcategorized into the following: infection-related death that did or did not represent a failure of antibacterial drug treatment. Table 9-14 summarizes the committee's results. A greater percentage of patients in the cefiderocol group than in the BAT group, respectively, had infection-related death with treatment failure (15.8% vs. 8.2%) but also death due to underlying co-morbidity (9.9% vs. 4.1%).

Table 9-14: Adjudication Committee Results for Causes of Death in the CREDIBLE-CR Trial

Cause of Death	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)	Difference (%)	95% CI
Overall mortality through Day 49	34 (33.7)	10 (20.4)	13.3	-1.3 to 27.8
Underlying comorbidity	10 (9.9)	2 (4.1)	5.8	-2.2 to 13.9
Infection-related death with treatment failure	16 (15.8)	4 (8.2)	7.7	-2.8% to 18.1
Infection-related death without treatment failure	1 (1.0)	1 (2.0)	-1.1	
Infection other than original Gram-negative infection	4 (4.0)	2 (4.1)	-0.1	
Drug-related adverse event	0 (0.0)	0 (0.0)	0.0	
Iatrogenic cause	0 (0.0)	0 (0.0)	0.0	
No unanimous vote*	3 (3.0)	0 (0.0)	3.0	
Not assessed by the committee	0 (0.0)	1 (2.0)	-2.0	

Source: Adapted from Table 1: Applicant Adjudication Committee results, Statistical Reviewer and Medical Officer

* Two cases not directly related to the original infection and 1 directly related to the original infection per committee; no unanimous vote on subcategory.

In addition to the 16 cases in which infection-related death was due to failure of cefiderocol treatment, there were 5 additional deaths possibly related to a lack of efficacy. Table 13-1 in the Appendix shows a detailed summary of deaths and the 'patient #' corresponds to the '#' listed in this table. Two deaths listed in the 'no unanimous vote' category in Table 9-14 were related to sepsis as a cause of death per the investigator

(patient #3 and #33). Two deaths that were considered related to an ‘underlying comorbidity’ were associated with a 4-fold MIC increase in the baseline pathogen during cefiderocol treatment with death possibly related to the original Gram-negative infection (patient #15 and #34). Another death categorized as ‘infection other than original Gram-negative infection’ involved discontinuation from the study due to SAEs of septic shock for which rescue antibacterial drugs were given (patient #14).

In the BAT group, one additional death categorized as ‘infection other than the original Gram-negative infection’ involved discontinuation of BAT on Day 2 for failure after which rescue antibacterial drugs were given for septic shock (patient #7).

Discontinuations

Treatment discontinuations due to AEs occurred in a greater number of patients who received cefiderocol as compared to BAT as noted in Table 9-15.

Table 9-15: Treatment Discontinuations due to TEAEs in CREDIBLE-CR Trial

Preferred Term	Cefiderocol N = 101 n (%)	BAT N = 49 n (%)
Any Discontinuation	10 (9.9)	3 (6.1)
Septic shock	4 (4.0)	0
Transaminases increased*	2 (2.0)	0
Cardiac arrest	1 (1.0)	0
Drug eruption	1 (1.0)	0
Hyponatraemia	1 (1.0)	0
Pyrexia	1 (1.0)	0
Respiratory failure	1 (1.0)	0
Anaphylactic reaction	0	1 (2.0)
Endocarditis	0	1 (2.0)
Status epilepticus	0	1 (2.0)

Source: Medical Officer * includes AST and ALT increased

Cefiderocol was discontinued in three patients due to AEs (pyrexia, drug eruption, and transaminitis increased) which were considered related to study drug per the investigator. Pyrexia (maximum temperature of 38.1°C) occurred on Day 12 and resolved 4 days after cefiderocol discontinuation. Drug eruption (maculopapular rash with eosinophilia) occurred on Day 6 and multiple treatments (including intramuscular steroids) were given; the rash resolved 18 days after cefiderocol discontinuation. Transaminitis increased is described in the hepatobiliary section. BAT was discontinued in two patients due to AEs (anaphylaxis and status epilepticus) which were considered related to study drug per the investigator.

Seven patients in the cefiderocol group and 1 in the BAT group who had a treatment discontinuation due to an AE also died. Three patients with septic shock died; one also

had multi-organ failure and death was considered to be related to treatment failure per the adjudication committee (patient #25, Table 13-1). Another death considered to be related to treatment failure occurred in the patient with transaminases increased (patient #12). Death was attributed to underlying comorbidities (atrial fibrillation, cerebrovascular accident, and hypertension) in a patient who had a cardiac arrest after treatment with furosemide for acute pulmonary congestion on Day 3 (patient #29). Another death attributed to underlying comorbidities occurred in a patient who developed hyponatremia on Day 2 (sodium 122 mEq/L) in the setting of an intracerebral hemorrhage treated with mannitol and furosemide (patient #26). Death due to an aspiration pneumonia that was considered ‘not related to the original infection’ occurred in the patient who had pyrexia above (patient #4). In the BAT group, death was considered to be related to treatment failure in the patient who developed status epilepticus on Day 13 (patient # 9).

Serious Adverse Events

Serious Adverse Events (SAEs) occurred in a slightly greater number of cefiderocol-treated patients as compared to BAT-treated patients as noted in Table 9-16, below. Individual patients experienced more than one SAE. More than 50% of the SAEs in either group occurred within 7 days of the last treatment. Thirty-four of the 50 patients in the cefiderocol group who developed SAEs had an outcome of death, and the remaining 16 patients had SAEs which recovered or resolved. Any cefiderocol-treated patient with a non-resolving SAE had a subsequent fatal outcome. Patients in the cefiderocol group with resolved SAEs associated with an action taken of ‘dose reduction’ or ‘drug withdrawal’ included pancreatitis, transaminases increased, and septic shock. Pancreatitis occurred in a patient with a history of pancreatic neuroendocrine tumor and pancreatectomy (amylase increased to 50 U/L, lipase was not reported).

Eight of the 23 patients in the BAT group who developed SAEs had an outcome of death. In the remaining 15 BAT-treated patients, 10 had resolved/resolving SAEs and 5 had non-resolving SAEs.

Table 9-16: Serious Adverse Events in CREDIBLE-CR Trial

System Organ Class/ Preferred Term	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
Any SAE	50 (49.5)	23 (46.9)
Infections and infestations	29 (28.7)	11 (22.5)
Septic shock	12 (11.9)	6 (12.2)
Pneumonia (includes pneumonia bacterial)	6 (5.9)	1 (2.0)
Bacteremia	3 (3.0)	0
Sepsis	3 (3.0)	0
Enterococcal infection or bacteremia	3 (3.0)	0
Bacterial infection (other Gram-positive infection)	1 (1.0)	0
Empyema	1 (1.0)	1 (2.0)

Osteomyelitis (includes acute osteomyelitis)	1 (1.0)	1 (2.0)
Renal Abscess	1 (1.0)	0
Systemic candida	1 (1.0)	0
Urinary tract infection	1 (1.0)	0
Urosepsis	1 (1.0)	0
Device-related infection	0	1 (2.0)
Endocarditis	0	1 (2.0)
Meningitis	0	1 (2.0)
Necrotising fasciitis	0	1 (2.0)
General disorders and administration site conditions	7 (6.9)	3 (6.1)
Pyrexia	3 (3.0)	0
Multi-organ failure	2 (2.0)	2 (4.1)
Sudden death	1 (1.0)	0
Chills	1 (1.0)	0
General physical health deterioration	0	1 (2.0)
Respiratory, thoracic and mediastinal disorders	7 (6.9)	2 (4.1)
Respiratory failure (includes acute respiratory failure)	3 (3.0)	1 (2.0)
Pneumonia aspiration	2 (2.0)	0
Obstructive airways disorders	1 (1.0)	0
Chronic obstructive pulmonary disease	1 (1.0)	0
Respiratory arrest	0	1 (2.0)
Cardiac disorders	6 (5.9)	4 (8.2)
Cardiac arrest	4 (4.0)	2 (4.1)
Bradycardia	1 (1.0)	1 (2.0)
Cardiac failure congestive	1 (1.0)	0
Myocardial infarction	1 (1.0)	0
Pulseless electrical activity	0	1 (2.0)
Renal and urinary disorders	6 (5.9)	2 (4.1)
Acute kidney injury	3 (3.0)	2 (4.1)
Oliguria (includes anuria)	2 (2.0)	0
Nephrolithiasis	1 (1.0)	0
Gastrointestinal disorders	5 (5.0)	0
Gastrointestinal hemorrhage (includes lower gastrointestinal hemorrhage)	2 (2.0)	0
Abdominal pain (includes abdominal pain upper)	2 (2.0)	0
Intestinal ischemia	1 (1.0)	0
Pancreatitis	1 (1.0)	0
Small intestinal obstruction	1 (1.0)	0

Investigations	5 (5.0)	3 (6.1)
Liver function test abnormal (includes transaminases increased)	5 (5.0)	3 (6.1)
Hepatobiliary disorders	3 (3.0)	0
Chronic hepatic failure	1 (1.0)	0
Hepatic failure	1 (1.0)	0
Hepatitis	1 (1.0)	0
Metabolism and nutrition disorders	3 (3.0)	1 (2.0)
Metabolic acidosis	2 (2.0)	1 (2.0)
Hyponatremia	1 (1.0)	0
Nervous system disorders	3 (3.0)	2 (4.1)
Dizziness	1 (1.0)	0
Hypoaesthesia	1 (1.0)	0
Neurological decompensation	1 (1.0)	0
Paraesthesia	1 (1.0)	0
Quadriplegia	0	1 (2.0)
Status epilepticus	0	1 (2.0)
Vascular disorders	2 (2.0)	2 (4.1)
Hypotension	2 (2.0)	1 (2.0)
Shock	1 (1.0)	1 (2.0)
Blood and lymphatic system disorders	1 (1.0)	1 (2.0)
Anemia	0	1 (2.0)
Febrile neutropenia	1 (1.0)	0
Neoplasms benign, malignant and unspecified	1 (1.0)	0
Lung neoplasm malignant	1 (1.0)	0
Immune system disorders	0	1 (2.0)
Anaphylactic reaction	0	1 (2.0)

Source: Medical Officer, Adapted from Table 26: CREDIBLE-CR Study Summary

Common Treatment-Emergent Adverse Events

Common TEAEs occurred in a slightly greater number of BAT-treated patients as compared to cefiderocol-treated patients. The most frequently (>10% of subjects in the cefiderocol group) reported TEAEs were diarrhea, elevated liver tests, and pyrexia. TEAEs with an incidence greater in the cefiderocol than in the BAT group are presented in Table 9-17. TEAEs that were more common in the cefiderocol group and not generally considered complications of treatment with antibacterial drugs (i.e. diarrhea, candidiasis) are discussed below.

Preferred Term	Cefiderocol (N=101)	BAT (N=49)
----------------	------------------------	---------------

	n (%)	n (%)
Any TEAE	92 (91.1)	47 (95.9)
Diarrhea	19 (18.8)	6 (12.2)
Elevated liver tests*	18 (17.8)	6 (12.2)
Pyrexia	14 (13.9)	6 (12.2)
Decubitus ulcer	10 (9.9)	4 (8.2)
Pneumonia*	9 (8.9)	2 (4.1)
Candidiasis*	9 (8.9)	3 (6.1)
Hypomagnesemia*	9 (8.9)	4 (8.2)
Anemia	8 (7.9)	2 (4.1)
Fluid overload*	8 (7.9)	3 (6.1)
Constipation	8 (7.9)	3 (6.1)
Hypotension	8 (7.9)	3 (6.1)
Pleural effusion	8 (7.9)	1 (2.0)
Dyspnea	7 (6.9)	2 (4.1)
Nausea	7 (6.9)	2 (4.1)
Chest pain*	7 (6.9)	0
Oliguria*	5 (5.0)	2 (4.1)
Agitation	5 (5.0)	2 (4.1)

Table 9-17: TEAEs with Incidence \geq 5% that Occurred More Frequently in the Cefiderocol Treatment Arm than in BAT in the CREDIBLE-CR Trial

Source: Medical Officer

*Elevated liver tests include AST, ALT, transaminases increased, liver function test abnormal, hepatic function abnormal; pneumonia includes pneumonia bacterial; candidiasis includes candida infection, systemic candida, candiduria; hypomagnesemia includes blood magnesium decreased; fluid overload includes peripheral edema, localized edema, peripheral swelling; chest pain includes chest discomfort; oliguria includes anuria

Pneumonia

The cefiderocol group had more than twice the incidence of patients with pneumonia TEAEs as compared to BAT. This difference persisted across outcomes of increasing severity, such as SAEs and deaths, Table 13-1. Of the 9 patients treated with cefiderocol who experienced a TEAE of pneumonia, only one survived but required antibacterial drugs for clinical failure at TOC for *P. aeruginosa* and *S. maltophilia* VABP (patient # (b) (6), Table 9-12).

The 8 patients who received cefiderocol who experienced a TEAE of pneumonia with a fatal outcome were examined in greater detail. Five patient deaths due to pneumonia were directly related to the original clinical diagnosis of HABP/VABP/HCABP (also considered ‘infection-related deaths due to treatment failure per the adjudication committee, patients # 11, 17, 18, 21, and 22).

Three patients who received cefiderocol with a fatal TEAE of pneumonia had a new respiratory pathogen identified or a concomitant respiratory pathogen that persisted. Patient #19 had recurrence of *A. baumannii* HABP and a new pathogen (*P. mirabilis*) in the sputum culture at FUP (investigator considered death due to worsening *A. baumannii* or *P. mirabilis* pneumonia). Patient #20 had a new pathogen (*C. meningosepticum*) in sputum culture and worsening pneumonia on Day 4. Lastly, patient #30 had a clinical diagnosis of *K. pneumoniae* BSI but also had *A. baumannii* and methicillin-susceptible *Staphylococcus aureus* in tracheal cultures on Day 1 for which vancomycin and cloxacillin was given. At TOC, *A. baumannii* persisted in tracheal cultures, additional antibacterial drugs and a tracheostomy was required for prolonged mechanical ventilation.

Chest pain

Seven patients in the cefiderocol group as compared to none in the BAT group experienced chest pain or chest discomfort. As noted in the Applicant's study summary, the majority of events of chest pain appeared to be non-cardiovascular in origin and likely unrelated to cefiderocol treatment. One patient had chest pain 1 day prior to an episode of asystole from which she recovered, but then another episode of asystole 8 days later, which caused death (patient # 28).

Fluid overload

Eight patients in the cefiderocol group as compared to 3 in the BAT group experienced fluid overload (includes peripheral edema or swelling). The cefiderocol-treated patients either had prior history of fluid overload or underlying comorbidities associated with fluid overload (cirrhosis, burn injury). Of note, the CREDIBLE-CR protocol recommended that the solution volume of infusion of cefiderocol was at least 100 mL and that dilution volumes greater than 100 mL could be used, if deemed necessary by the investigator, to reduce any emerging symptoms related to nausea or infusion site issues, e.g., pain, swelling. The actual volume of infusion in individual patients was unknown.

Adverse Events of Special Interest and Submission Specific Safety Issues

Hepatobiliary

Hepatic TEAEs occurred in 30 (29.7%) of cefiderocol-treated patients and 7 (14.3%) of BAT-treated patients. A summary of drug-related hepatic disorders TEAEs by SMQ and PT is noted in Table 9-18.

Table 9-18 is presented on the following page.

Table 9-18: Hepatic TEAEs in the CREDIBLE-CR Trial

SMQ/PT	Cefiderocol N=101 n (%)	BAT N=49 n (%)
Drug related hepatic disorders - comprehensive search	30 (29.7)	7 (14.3)
Alanine aminotransferase increased	7 (6.9)	0
Aspartate aminotransferase increased	8 (7.9)	4 (8.2)
Liver function test abnormal	8 (7.9)	4 (8.2)
Gamma-glutamyltransferase increased	2 (2.0)	0
Ascites	2 (2.0)	0
Blood bilirubin increased	2 (2.0)	1 (2.0)
Hepatic function abnormal	2 (2.0)	0
Hypoalbuminaemia	2 (2.0)	0
International normalized ratio increased	2 (2.0)	1 (2.0)
Blood alkaline phosphatase increased	2 (2.0)	0
Hepatic cirrhosis	1 (1.0)	0
Hepatic failure	1 (1.0)	0
Hepatitis	1 (1.0)	0
Hepatocellular injury	1 (1.0)	0
Hepatomegaly	1 (1.0)	0
Hyperbilirubinemia	1 (1.0)	0
Transaminases increased	1 (1.0)	0
Chronic hepatic failure	1 (1.0)	0
Hepatic cirrhosis	1 (1.0)	0
Hepatic enzyme increased	0	1 (2.0)

SMQ - Standardized MedDRA Query; PT – preferred term

Source: Table 3.1 Applicant response to information request 18 July 2019

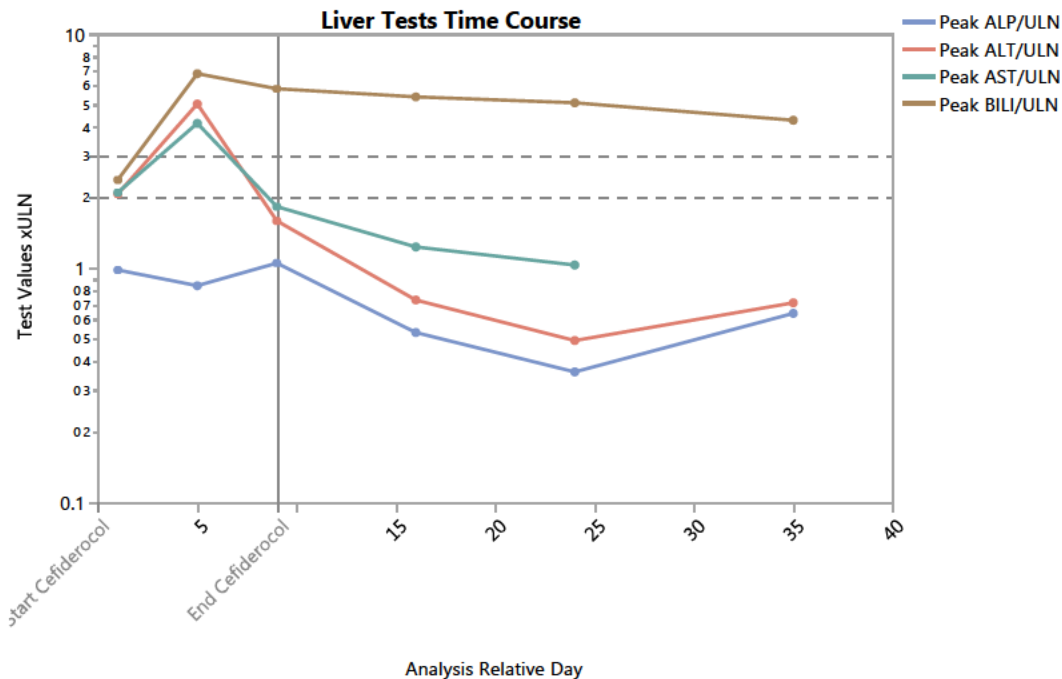
Increases in AST and ALT led to the discontinuation of cefiderocol in two patients. One patient with no history of liver disease with baseline increased liver tests (AST >1x to < 2x ULN, ALP > 2x ULN) receiving concomitant medications (atorvastatin, tramadol, fosfomycin, polymyxin, pregabalin) had an AST and ALT > 5x ULN on Day 6 which resolved by Day 35. This AE was considered treatment-related by the investigator as cefiderocol was the only new medication and the hepatic ultrasound was negative. Another patient with a medical history of an autoimmune disorder and baseline increased liver tests (AST >1x to < 2x ULN, ALP >3x ULN) receiving multiple concomitant medications had an AST and ALT > 3x ULN on Day 19 which decreased by Day 26 after cefiderocol discontinuation on Day 20. The TB was also >10x ULN on Day 19 and remained elevated until death (patient #12). Of note, the alkaline phosphatase was >2x ULN, thus Hy's Law criteria were not met.

Maximum post-baseline increases in AST or ALT > 3 to 5x ULN were observed in 17.7% (17/96) and 2.1% (1/48) and AST or ALT > 5 to 20x ULN were observed in 10.4% (10/96) and 14.6% (7/48) and AST or ALT > 20x ULN were observed in 4.2% (4/96) and 0% (0/48) in the cefiderocol and BAT groups, respectively. The maximum post-baseline increases in total bilirubin > 2x ULN were observed in 15.1% (14/92) and 12.5% (6/48) of cefiderocol and BAT groups, respectively. Maximum post-baseline increases in PT-INR were similar in both groups.

Hy's Law

One patient in the cefiderocol group fulfilled the laboratory criteria for Hy's Law, i.e. ALT > 3x ULN, total bilirubin > 2x ULN, and alkaline phosphatase < 2x ULN. The time course of elevated liver tests is noted in Figure 7 below. Pertinent medical history included chronic hepatitis B with unknown treatment status/recent serology and concomitant medications (propofol, metamizole, metoclopramide, levetiracetam, levofloxacin, and others). Total bilirubin remained elevated and a fatal SAE of refractory hepatic failure was reported on Day 34.

Figure 7: Liver Tests Time Course for Patient with Hy's Law in CREDIBLE-CR Trial



Source: Medical Officer

Another patient met criteria for Hy's Law based on ALT and total bilirubin, but post-Day 1 values of alkaline phosphatase were missing (Day 1 alkaline phosphatase was <2x ULN). The patient had no prior history of liver disease but had an elevated ALT, AST

and total bilirubin > 2x ULN at baseline (patient # 26). Eight additional patients in the cefiderocol group had concomitant elevations in AST or ALT >3x ULN and total bilirubin > 2x ULN, however the alkaline phosphatase was >2x ULN. Of note, 7 of these 8 patients had a fatal outcome (#7, 11, 12, 13, 14, 27, 32). Other than patient #32 who had a history of cholangiocarcinoma and hepatitis, none had a history of liver disease (two had cancer with metastasis to liver).

Renal

The post-baseline changes in serum creatinine are noted in Table 9-19. Colistin-related renal toxicity was noted in the BAT group.

Table 9-19: Post-baseline changes in serum creatinine in the CREDIBLE-CR Trial

Post-baseline Change in Creatinine	Cefiderocol (N =101) n (%)	BAT (N = 49) n (%)
Serum Cr 1.5x to 2x from baseline by TOC	15 (14.9)	7 (14.3)
Serum Cr 2x to 3x from baseline by TOC	5 (5.0)	8 (16.3)
Serum Cr >3x from baseline or (baseline \geq 4 mg/dL and serum Cr increase \geq 0.5 mg/dL)	1 (1.0)	2 (4.1)

Source: Table 4.1 Applicant response to information request 18 July 2019

Hematology

Observational studies show that iron metabolism disorders (decreased availability of iron and elevated ferritin) can occur within the first few days in the ICU setting. Iron metabolism disorders may potentially contribute to the anemia observed in ICU patients⁴. As cefiderocol has a siderophore-based mechanism, hematology-related TEAEs were investigated. Overall, 13.9% and 6.1% patients in the cefiderocol and BAT groups, respectively, had TEAEs related to anemia or iron-related investigations,

Table 9-20. In both treatment groups combined, 10 patients with anemia had no prior history of anemia, but most had predisposing conditions such as malignancy and chronic kidney disease. Of these 10 patients, 2 in the cefiderocol group and 1 in the BAT had an outcome of 'not recovered.' One cefiderocol-treated patient had progression of anemia from baseline to Day 34 (8.0 to 4.1 g/dL) despite several blood transfusions, iron and erythropoietin; the patient died from sepsis on Day 36. Three other patients in the cefiderocol group with anemia TEAEs also died while both patients in the BAT group survived.

Table 9-20: Anemia-related TEAEs in the CREDIBLE-CR Trial

System Organ Class/ Preferred Term	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)
Subjects with adverse events	14 (13.9)	3 (6.1)
Blood and lymphatic system disorders	10 (9.9)	3 (6.1)
Anemia	8 (7.9)	2 (4.1)
Anemia of chronic disease*	1 (1.0)	1 (2.0)
Normochromic normocytic anemia*	1 (1.0)	0
Investigations	4 (4.0)	0
Blood iron decreased	1 (1.0)	0
Hemoglobin decreased	1 (1.0)	0
Serum ferritin increased	1 (1.0)	0
Transferrin decreased	1 (1.0)	0
Transferrin saturation decreased	2 (2.0)	0

Source: Table 4.2 Applicant response to information request 18 July 2019

* history of anemia or low hemoglobin at baseline

Overall, maximum post-baseline decreases in hemoglobin were similar in both treatment groups, Table 9-21. Six patients in the cefiderocol group had worsening from grade 0 or 1 to 3 based on the common terminology criteria for adverse events (CTCAE) grading system. Maximum decreases in hemoglobin occurred at an average of 21 days (range 9 to 41 days). All 6 patients had a history of anemia or a predisposing condition such as malnutrition and 5 had a fatal outcome. One of the two patients in the BAT group with worsening from grade 1 to 3 had a fatal outcome.

Table 9-21: Maximum Post-baseline Decreases in Hemoglobin in the CREDIBLE-CR Trial

Baseline hemoglobin Grade	Post-baseline Hemoglobin Grade	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
	Any Worsening Grade	43 (42.6)	24 (49.0)
Grade 0:	Grade 1	2 (2.0)	0
	Grade 2	1 (1.0)	0
	Grade 3	1 (1.0)	0
Grade 1:	Grade 2	13 (12.9)	9 (18.4)
	Grade 3	5 (5.0)	2 (4.1)
Grade 2:	Grade 3	21 (20.8)	13 (26.5)

Source: Medical Officer. CTCAE Grade 0: Hgb \geq LLN to \leq ULN, Grade 1: Hgb $<$ LLN - 100 g/L, Grade 2: Hgb $<$ 100 - 80g/L, Grade 3: Hgb $<$ 80 g/L

10 APEKS-NP Trial

10.1 Study Design

Cefiderocol is also being developed for the treatment of HABP/VABP. The Applicant has recently completed a Phase 3 trial titled “A Multicenter, Randomized, Double-blind, Parallel-group, Clinical Study of S-649266 Compared with Meropenem for the Treatment of Hospital-acquired Bacterial Pneumonia, Ventilator-associated Bacterial pneumonia, or Healthcare-associated Bacterial Pneumonia Caused by Gram-negative Pathogens,” trial APEKS-NP.

Data from this study have not yet been submitted for review. Only top line mortality results have been submitted to the Agency.

The trial enrolled subjects ≥ 18 years old who met clinical diagnostic criteria for HABP, VABP, or HCABP.

All patients were to have at least one of the following clinical criteria:

- New onset of worsening cough, dyspnea, tachypnea, expectorated sputum production, or requirement for mechanical ventilation.
- Hypoxemia.
- Need for acute changes in ventilator support system.
- New onset of or increase in suctioned respiratory secretions.

In addition, patients were to have at least one of the following signs:

- Documented fever.
- Hypothermia.
- Elevated WBC count.
- Leukocytosis.
- Leukopenia.
- Greater than 15% immature neutrophils (bands) noted on peripheral blood smear.

The pneumonia diagnosis also required a chest x-ray or CT scan showing the presence of a new or progressive infiltrate(s) suggestive of bacterial pneumonia.

The exclusion criteria disallowed subjects with known or suspected community-acquired pneumonia, atypical pneumonia, viral pneumonia, or chemical pneumonia, and patients with evidence of Gram-positive pneumonia or anaerobic bacterial pneumonia. Subjects with a carbapenem-resistant pathogen were excluded (subjects with a carbapenem-resistant pathogen identified after randomization were evaluated clinically before discontinuation of study treatment).

The protocol excluded subjects who received potentially effective antibacterial therapy for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization. Patients in both treatment groups were to receive linezolid for the full duration of therapy to provide coverage for MRSA. The protocol did not allow concomitant use of systemic antibacterial drugs with Gram-negative activity, aerosolized

antibacterial drugs, probenecid, methotrexate, procainamide, or monoamine oxidase inhibitors.

Subjects were randomized in a 1:1 ratio to cefiderocol or meropenem, stratified by infection type (HABP, VABP, or HCABP) and APACHE II score (≤ 15 and ≥ 16). Cefiderocol dosing was the same as in the cUTI Trial, except that the infusion was given over 3 hours. Meropenem was dosed at 1 gram over 3 hours every 8 hours. The study drug (cefiderocol or meropenem) was to be given for 7-14 days, with possible extension of up to Day 21 if a clear reason was documented by the investigator.

Study visits included an early assessment (Day 3-4), an end of treatment (EOT) visit, a test of cure (TOC) visit 7 ± 2 days after the EOT visit, and a follow-up (FUP) visit 14 ± 3 days after the EOT visit.

The primary analysis population for efficacy was the modified intent-to-treat population. This analysis population excluded subjects with bacterial pneumonia caused by only Gram-positive pathogens or anaerobic pathogens.

The primary efficacy endpoint was Day 14 all-cause mortality. This was a noninferiority trial with a margin of 12.5% on the risk difference scale.

The study was monitored by a Data Safety Monitoring Board and completed enrollment with a final total sample size of 300 subjects.

10.2 Mortality Results

The following table shows the all-cause mortality results. These data have not been verified by the Agency.

Table 10-1: APEKS-NP all-cause mortality results by time point

	Cefiderocol n/N (%)	Meropenem n/N (%)	Difference (%)	95% CI
Day 14 ACM	19/148 (12.8)	17/149 (11.4)	1.4	-6.0 to 8.7
Day 28 ACM	31/146 (21.2)	30/149 (20.1)	1.1	-8.0 to 10.3
Overall ACM	39/145 (26.9)	34/149 (22.8)	4.1	-5.6 to 13.8

Source: Applicant advisory committee briefing materials, Table 42

11 Summary

Cefiderocol is a siderophore cephalosporin with activity against several Gram-negative bacteria. Surveillance data provided show that the cefiderocol MIC₉₀ values for many Gram-negative organisms are ≤ 2 mcg/mL. However, there are *A. baumannii*, *S. maltophilia*, *P. mirabilis*, *M. morganii*, *E. cloacae* and *S. marcescens* isolates with MIC values ≥ 16 mcg/mL. Activity of cefiderocol has been demonstrated in murine models of infection (systemic infection, neutropenic lung infection, neutropenic thigh

infection, and immunocompetent urinary tract infection). In the neutropenic thigh infection model, cefiderocol was active against most Gram-negative bacterial isolates (*P. aeruginosa*, *A. baumannii*, *E. coli*, and *K. pneumoniae*) with cefiderocol MIC of ≤ 4 mcg/mL. Post-exposure increases in cefiderocol MICs were reported in *in vitro*, *in vivo*, and clinical studies.

The clinical data package submitted to the NDA includes a randomized, active controlled noninferiority trial in cUTI comparing cefiderocol to imipenem-cilastatin (IMP), a descriptive study (CREDIBLE-CR) comparing cefiderocol to best available therapy (BAT) in patients with infections due to carbapenem-resistant organisms and top-line results from a recently completed active controlled noninferiority trial in HABP/VABP (APEKS-NP) comparing cefiderocol to meropenem.

In the cUTI trial, clinical and microbiologic success rates at the test of cure visit were 183/252 (72.6%) in the cefiderocol group and 65/119 (54.6%) in the IMP group; difference in success rates of 18.6%, 95% CI, 8.2% to 28.9%. Clinical response rates were similar between the treatment groups and the difference in overall response was driven primarily by the microbiologic success component of the composite endpoint. In the safety database of 300 subjects who received the proposed cefiderocol dose of 2 g every 8 hours for 7-14 days, the most common AEs were diarrhea, hypertension, constipation, rash, and infusion site reactions. Cephalosporin-class AEs were noted in subjects in the cefiderocol arm, including hypersensitivity reactions, *C. difficile* colitis, seizure, and hepatobiliary adverse events. There was 1 death in the cefiderocol group that appeared to be unrelated to the drug compared to none in the IMP group.

The CREDIBLE-CR study was a descriptive study with no pre-specified hypothesis testing. The study completed enrollment during the NDA review; datasets were submitted to the Agency for review and the clinical study report was not submitted. In this trial, patients with HABP/VABP, cUTI, and BSI/sepsis due to carbapenem-resistant organisms were randomized to receive cefiderocol or BAT, of which 66% were colistin-based regimens. All-cause mortality was higher in the cefiderocol group compared to the BAT group at Day 14 (18.8% versus 12.2%) and Day 28 (24.8% versus 18.4%) respectively. The greatest mortality difference disfavoring cefiderocol was noted in the HABP /VABP /HCABP subgroup, followed by the BSI/sepsis subgroup. An independent adjudication committee determined that a greater percentage of patients in the cefiderocol group than in the BAT group had infection-related death with treatment failure (15.8% vs. 8.2%), but also noted an imbalance in death due to underlying co-morbidities (9.9% vs. 4.1%). Pharmacokinetic analysis did not show an association between cefiderocol exposure and mortality. The most frequent TEAEs that lead to death in the cefiderocol group were generally infection-related, such as septic shock, pneumonia, sepsis, and bacteremia. Hepatic TEAEs occurred in 30 (29.7%) of cefiderocol-treated patients and 7 (14.3%) of BAT-treated patients.

APEKS-NP was a randomized, prospective, double-blind, active-controlled non-inferiority trial comparing cefiderocol to meropenem for the treatment of HABP/VABP. This trial also completed enrollment during the NDA review and only top-line mortality

results have been submitted to the Agency. In the ITT population, the Day 14 mortality rates reported are 12.8% in the cefiderocol group and 11.4% in the meropenem group, treatment difference 1.4% and 95% CI, -6.0% to 8.7%. The Day 28 mortality rates reported are 21.2% in the cefiderocol group and 20.1% in the meropenem group, treatment difference 1.1% and 95% CI, -8.0% to 10.3%. The data have not been reviewed or verified by the Agency.

In summary, while the safety and efficacy of cefiderocol have been demonstrated for the treatment of cUTI, higher mortality in cefiderocol-treated patients was observed in a trial in critically ill patients with a variety of infections due to carbapenem-resistant organisms.

In the cUTI trial that did not include patients with infections due to carbapenem-resistant organisms, there was a finding of statistical superiority of cefiderocol compared to IMP that seems to be driven primarily by the differences in microbiologic success rates. The overall mortality in this trial was low, with only one death reported in a cefiderocol-treated patient. However, in a descriptive study in patients with infections due to carbapenem-resistant organisms, the all-cause mortality was higher in cefiderocol-treated subjects compared to those treated with BAT, majority of which were colistin-based regimens.

While no specific reason for the imbalance in mortality could be identified, it appears that some of the deaths were related to progression of infection/lack of clinical response and were more common in patients with infections due to organisms such as *A. baumannii*, *S. maltophilia*, and *P. aeruginosa*. Whether this difference in mortality is a chance finding or truly reflects a deficit in the activity of cefiderocol in critically ill patients is unclear. In a third trial in patients with HABP/VABP due to carbapenem-susceptible organisms, top-line results suggest that the mortality rates in cefiderocol and comparator-treated patients are similar. These results have not been verified by the Agency.

12 Points for Advisory Committee Discussion

- Please discuss your assessment of the finding of increased mortality in the CREDIBLE-CR study in the overall risk benefit considerations for cefiderocol and provide recommendations for labeling and/or need for additional studies.
- Has the Applicant provided substantial evidence of the efficacy and sufficient evidence of the safety of cefiderocol for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis in patients with limited or no alternative treatment options?
 - a. If yes, please provide any recommendations regarding labeling.
 - b. If no, what additional studies/analyses are needed?

13 Appendix

Table 13-1: Summary of 44 Fatal Cases through Day 49 in the CREDIBLE-CR Trial

#	Subject ID	Age/ Sex	APACHE score	Co- morbidities	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
Deaths in cUTI Patients who Received Cefiderocol											
1	(b) (6)	83/ M	20	DM, COPD, CKD, indwelling catheter	Oliguria, Anuria	5	3	Only + PCR: <i>K. pneumoniae</i>	Death	Renal failure SAE on Day 4; Family withdrew consent for study	No
2	(b) (6)	92/ M	11	AF, COPD, CM, indwelling catheter	MOF, Shock	4	0	<i>K. pneumoniae</i>	Death	Hypotension, oliguria SAE on Day 3; Family withdrew consent for treatment	Yes
3	(b) (6)	78/F	27	Anoxic brain injury, MV disease, CAD, CKD	Septic shock	2	0	<i>P. aeruginosa</i>	Death	Found dead with dilated pupils, probable cause of death was sepsis per investigator	Yes†
4	(b) (6)	77/ M	6	DM, CVA, HTN, Neurogenic bladder	Pneumonia aspiration	12	14	<i>P. aeruginosa</i>	Cure	Cefiderocol switched to piperacillin-tazobactam due to pyrexia on Day 12; Aspiration pneumonia SAE on Day 17	No‡
Deaths in HABP/VABP/HCABP Patients who Received Cefiderocol											
5	(b) (6)	46/ M	13	DM, Down Syndrome, Chronic HBV, Asthma	Chronic hepatic failure	8	27	<i>K. oxytoca</i> (HABP)	Cure	Hy's Law and AKI on Day 4; liver tests improved after cefiderocol D/C; hospice for refractory liver failure	No

#	Subject ID	Age/ Sex	APACHE score	Co- morbidity	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
6	(b) (6)	70/ M	15	DM, COPD, CAD	Myocardial infarction	10	3	<i>S. maltophilia</i> (VABP)	Death	WBC, CRP increased, <i>S. maltophilia</i> in TA on Day 10 (4-fold increase in MIC to cefiderocol, colonization per Applicant); MI SAE on Day 12	No
7	(b) (6)	78/ M	17	AAA s/p repair	Septic shock	14	17	<i>A. baumannii</i> , <i>E.coli</i> , <i>K. pneumoniae</i> (HABP)	Failure	<i>E. faecium</i> BSI (daptomycin) & empyema on Day 19; 4-fold MIC increase (<i>K.pneumoniae</i>) on Day 23; Relapse at FUP	Yes
8	(b) (6)	68/ M	18	Esophageal CA, AF, CKD	Respiratory failure	6	6	<i>E. cloacae</i> (HABP)	Death	Study discontinuation due to respiratory failure SAE from HAP, increased liver tests. Family withdrew care.	Yes
9	(b) (6)	69/ M	13	DM, AF, CAD, COPD	Non- resolved sepsis	9	0	<i>A. baumannii</i> (VABP)	Death	4-fold MIC increase at Day 3; Elevated liver tests on Day 7; Failure and SAE of worsening sepsis at EOT	Yes
10	(b) (6)	65/ M	27	TB, lung adeno- carcinoma, COPD	Non- resolved sepsis	11	13	<i>A. baumannii</i> , <i>P. aeruginosa</i> (VABP)	Death	4-fold MIC increase (<i>A. baumannii</i>) at Day 10, cefiderocol D/c due to diarrhea and leukemoid reaction	Yes
11	(b) (6)	65/ M	24	AF, DM, COPD, vasculitis	Pneumonia bacterial	14	0	<i>A. baumannii</i> (HABP)	Death	4-fold MIC increase, worsening pneumonia at EOT	Yes
12	(b) (6)	45/ M	19	AF, Psoriasis, burn injury	Septic shock	19	20	<i>A. baumannii</i> (VAP)	Failure	4-fold MIC increase at TOC; <i>A. baumannii</i> BSI on Day 9; Cefiderocol D/c due to lack of efficacy on Day 10, colistin & tigecycline given	Yes

#	Subject ID	Age/ Sex	APACHE score	Co- morbidities	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
1 3	(b) (6)	64/ M	29	DM, CAD, PVD	Septic shock	4	0	<i>A. baumannii</i> (VABP) <i>K. oxytoca</i> (BSI)	Death	4-fold MIC increase, increased liver tests on Day 3	Yes
1 4		78/ M	19	COPD, Metastatic lung CA	Respiratory failure, Septic shock	10	9	<i>A. baumannii</i> , <i>S. maltophilia</i> (VABP)	Failure	Study withdrawal due to SAEs of septic shock, colistin & amp-sulbactam given	No
1 5		66/F	28	AF, Liver cirrhosis, chronic HBV, lymphoma	Septic shock	15	30	<i>A. baumannii</i> , <i>P. aeruginosa</i> (VABP)	Failure	4-fold MIC increase (<i>A.</i> <i>baumannii</i>) at EOT; Cefoperazone-sulbactam given on Day 18, colistin, imipenem- cilastatin on Day 23	No
1 6		47/ M	9	Alcoholic cirrhosis, HBV carrier	Septic shock, Hepatic failure	8	0	<i>A. nosocomialis</i> <i>C. indologenes</i> , <i>P. aeruginosa</i> , <i>S. maltophilia</i> (VABP)	Death	Clinical failure at Day 8. 4- fold increase in MIC to <i>S.</i> <i>maltophilia</i> at EOT, SAE of liver failure	Yes
1 7		71/F	23	HTN, Lung Adeno- carcinoma	MOF, Pneumonia	3	0	<i>A. nosocomialis</i> (VABP)	Death	SAEs of MOF, VAP aggravation and AKI on Day 2	Yes
1 8		54/ M	13	COPD, Metastatic lung CA	Pneumonia, Bacteraemia	15	3	<i>A. baumannii</i> (HABP)	Death	<i>A. baumannii</i> BSI developed; Cefiderocol D/c due to lack of efficacy on Day 14, colistin given	Yes
1 9		73/ M	18	DM, CVA, Colon CA	Pneumonia	14	23	<i>A. baumannii</i> (HABP)	Cure	MRSA in sputum cx on Day 1 (No TX until Day 5); Relapse at FUP; tracheostomy declined.	No

#	Subject ID	Age/ Sex	APACHE score	Co- morbidities	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
20	(b) (6)	86/F	24	HTN, CAD, CKD	AKI	5	0	<i>A. baumannii</i> (HABP)	Death	Clinical failure on Day 4; SAE of AKI/CRRT stopped for financial reasons	No
21	(b) (6)	71/ M	20	DM, HTN, Parkinson's	Pneumonia	3	0	<i>A. baumannii</i> (HABP)	Death	Septic shock on Day 1, clinical failure on Day 3	Yes
22	(b) (6)	80/F	25	DM, HTN, AF, CKD	Aggravated pneumonia	12	1	<i>K. pneumoniae</i> , <i>P. aeruginosa</i> (HABP)	Death	Family declined intubation for worsening pneumonia on Day 10	Yes
23	(b) (6)	84/F	22	HTN, Aortic aneurysm	Cardiac arrest, Septic shock	14	1	<i>S. maltophilia</i> (VABP)	Death	Cefiderocol D/c due to lack of efficacy; 4-fold MIC increase at EOT	Yes
Deaths in BSI/SEPSIS Patients who Received Cefiderocol											
24	(b) (6)	54/ M	2	Paraplegia, neurogenic bladder, epilepsy	Sudden death	22	21	<i>P. aeruginosa</i> (Sepsis due to SSTI)	Cure	Low APACHE and SOFA 0 during study; unexplained sudden death on Day 43	No
25	(b) (6)	64/F	13	Asthma, COPD, breast CA	Septic shock, MOF	9	2	Only PCR + <i>A.</i> <i>baumannii</i> (BSI: possible VAT)	Death	cefiderocol D/c on Day 9 due to SAE of shock; colistin, gentamicin, ceftazidime- avibactam given. New <i>A.</i> <i>baumannii</i> pneumonia on Day 11	Yes

#	Subject ID	Age/ Sex	APACHE score	Co- morbidities	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
26	(b) (6)	24/F	12	Traumatic fall: fractures, ICH	Hyponatrae mia	2	4	<i>A. baumannii</i> (BSI: IV line)	Death	Cefiderocol D/c on Day 2 due to hyponatremia and declared brain dead	No
27	(b) (6)	29/F	24	Metastatic Rectal CA	Septic shock	6	0	<i>A. baumannii</i> (BSI: unknown)	Death	Clinical failure and new carbapenem-resistant <i>K.pneumoniae</i> BSI on Day 4	Yes
28	(b) (6)	70/F	19	DM, AF, Renal failure, TEN	Cardiac arrest	14	5	<i>A. baumannii</i> (BSI: unknown)	Death	AKI requiring HD and candidemia on Day 10, VRE BSI on Day 18 (vancomycin before susceptibility result)	No
29	(b) (6)	79/ M	17	AF, Bladder CA, ileal conduit	Cardiac arrest	3	0	<i>K. pneumoniae</i> (BSI: cUTI or IV line)	Death	Indwelling line removed; Cefiderocol D/c on Day 3 after SAE of asystole	No
30	(b) (6)	70/ M	18	DM, CAD, Metastatic bladder CA	<i>Proteus</i> <i>mirabilis</i> BSI	22	26	<i>K. pneumoniae</i> (BSI: cUTI)	Cure	MSSA, <i>A. baumannii</i> in tracheal culture on Day 1(cloxacillin). Polymicrobial sepsis, VRE BSI at EOT; fungemia; <i>proteus</i> BSI on Day 43. Meropenem given Day 27 for <i>A. baumannii</i> (not eradicated).	No
31	(b) (6)	84/ M	18	DM, CHF, COPD CKD	CHF, Lung neoplasm malignant	22	14	Only PCR + <i>A.</i> <i>baumannii</i> (BSI: HABP)	Cure	Lung CA diagnosed on Day 2; chest x-ray unchanged at EOT; CHF exacerbation on Day 35	No

#	Subject ID	Age/ Sex	APACHE score	Co- morbidity	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
3 2	(b) (6)	47/F	14	Cholangio CA, hepatitis, venous repair	Septic shock, Metabolic acidosis, VRE	9	0	<i>K. pneumoniae</i> (BSI: cIAI)	Death	SAE of worsening hepatitis on Day 6/VRE BSI on Day 8 (cleared on Day 9 after Daptomycin)	No
3 3	(b) (6)	77/ M	29	HTN, Aortic aneurysm, CKD, ICH	Sepsis	8	28	<i>K. pneumoniae</i> (BSI: questionable HABP)	Cure	4-fold increase in MIC (1 in blood to >64 in sputum) at Day 18, Relapse at FUP; cause of death – sepsis due to HAP	No [‡]
3 4	(b) (6)	82/ M	23	TB, COPD, cholecystitis	Secretion obstruction, hemoptysis (related to VAT or history of TB)	9	18	<i>A. baumannii</i> (Sepsis due to VAT)	Cure	Worsening renal function on cefiderocol, improved after D/c, <i>A. baumannii</i> persistence in sputum at FUP, 4-fold MIC increase at Day 16	No
Deaths in cUTI Patients who Received Best Available Therapy											
1	(b) (6)	85/ M	14	BPH, nephrostomy tube, COPD	AKI, Metabolic acidosis, Respiratory arrest	7	0	<i>K. pneumoniae</i>	Death	BAT: colistin, Fosfomycin; ARF on Day 3 (related to colistin per investigator)	No
2	(b) (6)	62/ M	13	Alcoholic liver cirrhosis, ureterolithiasis	Aggravated septic shock	6	0	<i>P. aeruginosa</i>	Death	BAT: colistin; Failure on Day 4, MRSA BSI on Day5 (given vancomycin)	No
Deaths in HABP/VABP/HCABP Patients who Received Best Available Therapy											

#	Subject ID	Age/ Sex	APACHE score	Co- morbidity	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
3	(b) (6)	84/F	22	DM, HTN, CAD, ESRD	Cardio- pulmonary arrest	11	14	<i>K. pneumoniae</i> (VABP)	Failure	BAT: tigecycline, colistin; cardiac arrest on Day 11, D/c study due to lack of efficacy on Day 12, 4-fold MIC increase to tigecycline and colistin on Day 13	Yes
4	(b) (6)	74/ M	12	CAD, Lung adeno- carcinoma, partial lung resection	Bradycardia, cardiac arrest	9	5	<i>A. baumannii</i> , <i>E. asburiae</i> (VABP)	Death	BAT: trimethoprim- sulfamethoxazole, cipro; Clinical cure on Day 9	No
5	(b) (6)	57/ M	13	HTN, CAD, Liver cirrhosis	MOF	12	0	<i>K. pneumoniae</i> (HABP)	Death	BAT: colistin, imipenem- cilastatin; Clinical failure on Day 3, perineal <i>K. pneumoniae</i> SSTI on Day 7	No
6	(b) (6)	42/ M	14	HTN, ESRD, pancreatic tumor s/p resection	Acute respiratory failure, Cardiac arrest	12	1	<i>A. baumannii</i> (VABP)	Death	BAT: colistin, cefepime; Cefepime changed to meropenem (resistant) due to failure on Day 4	Yes
Deaths in BSI/Sepsis Patients who Received Best Available Therapy											
7	(b) (6)	77/ M	20	AF, CVA, CHF, Parkinson's	Septic shock, MOF	2	8	<i>A. baumannii</i> (BSI: unknown)	Death	BAT: colistin, sultamicillin; BAT D/c on Day 2 for failure, changed to tigecycline; <i>P.</i> <i>aeruginosa</i> BSI on Day 9, colistin, aztreonam, gentamicin for septic shock	No

#	Subject ID	Age/ Sex	APACHE score	Co- morbidity	AE associated with Death	Days of TX	Days from TX to death	CR Pathogen at Screening	Clinical Outcome by TOC	Description	Death Related to TX*
8	(b) (6)	73/F	22	Acute hepatic failure, AKI, Parkinson's disease	Septic shock	10	7	<i>K. pneumoniae</i> (BSI: unknown)	Death	BAT: colistin, fosfomycin; CRE BSI <i>P. stuartii</i> on Day 6, meropenem added on EOT; 4-fold MIC increase to colistin at Day 13	Yes
9	(b) (6)	69/ M	18	AF, RHD, CHF, CVA, colon CA	General physical health deterioration	15	9	<i>P. aeruginosa</i> (BSI: IV line)	Failure	BAT: ceftazidime/cipro; Failure based on changing cipro to colistin on Day 6; AKI, status epilepticus may have been related to BAT	Yes
10	(b) (6)	79/ M	26	HTN, AF, CHF, CKD	NA	13	30	<i>A. baumannii</i> <i>M. morganii</i> (Sepsis: IV line)	Death	BAT: colistin; IV line replaced on Day 3; Amp-sulbactam added (protocol deviation). Failure at EOT, but cleared BSI by Day 28	NA

* Death directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study and infection-related death represents a failure of study drug treatment as reported by the Sponsor's blinded adjudication committee.

† Death directly related to the Gram-negative infection, but no unanimous vote on subcategory: 2 experts considered death represented failure of study drug, 1 expert did not.

‡ Death not directly related to the Gram-negative infection, but no unanimous vote on subcategory: 2 experts considered death related to infection other than the original Gram-negative infection, 1 expert considered death was likely due to patient's underlying comorbidity.

Abbreviations: AAA – abdominal aortic aneurysm; AF – atrial fibrillation; AKI – acute kidney injury; BAT – best available therapy; BPH – benign prostatic hypertrophy; BSI – blood stream infection; CA – cancer; CHF – congestive heart failure; CKD – chronic kidney disease; CRP – C-reactive protein; COPD – chronic obstructive pulmonary disease; CVA – cerebrovascular accident; D/c – discontinuation; DM – diabetes mellitus; EOT – end of therapy; ESRD – end-stage renal disease; F – female; FUP -follow-up; HAP – hospital-acquired bacterial pneumonia; HTN -hypertension, ICH – intracranial hemorrhage; IHD – ischemic heart disease; IV – intravenous; M – male; MOF – multi-organ failure; MV – mitral valve; NA – not available; PCR – polymerase chain reaction, RHD – rheumatic heart disease; TA – tracheal aspirate; TB – tuberculosis; TEN – toxic epidermal necrolysis; TOC – test of cure; VABP – ventilator-associated bacterial pneumonia, VAT – ventilator-associated tracheobronchitis; VRE – vancomycin resistant enterococci.

14 References

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